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Iodine-Catalyzed Synthesis of Substituted Furans and Pyrans: Reaction Scope and Mechanistic Insights

Domenic P. Pace, Raphaël Robidas, Uyen P. N. Tran, Claude Y. Legault,* and Thanh Vinh Nguyen*

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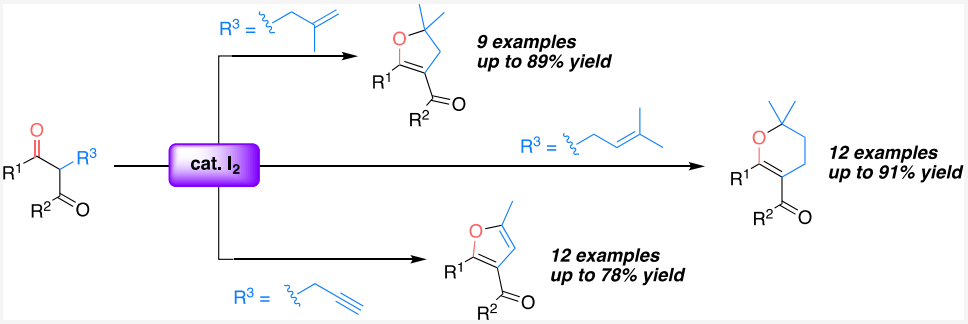

ABSTRACT: Substituted pyrans and furans are core structures found in a wide variety of natural products and biologically active compounds. Herein, we report a practical and mild catalytic method for the synthesis of substituted pyrans and furans using molecular iodine, a simple and inexpensive catalyst. The method described is performed under solvent-free conditions at an ambient temperature and atmosphere, thus offering a facile and practical alternative to currently available reaction protocols. A combination of experimental studies and density functional theory calculations revealed interesting mechanistic insights into this seemingly simple reaction.

INTRODUCTION

Molecular iodine, an environmentally friendly and inexpensive commodity chemical, has long been known not only as a versatile reagent but also as an efficient catalyst to promote a wide variety of chemical transformations.[1] Being the largest non-radioactive element in group 7 of the periodic table, iodine is also the least electronegative and the most polarizable halogen.[1c,2] These properties lead to its several oxidation states in several classes of synthetically valuable organoiodines.[3] In the elemental form, its ability to interact with oxygen-containing functional groups has been exploited to design efficient iodine-catalyzed organic reactions such as Michael, aldol, esterification, and a range of cycloaddition reactions.[1] Realization of the full catalytic potential of molecular iodine has consistently been a topic of interest in the past decades.[1d]

Recently, we discovered the intriguing catalytic activity of molecular iodine in promoting carbonyl−olefin metathesis.[4] However, in the course of that study, we noticed an unexpected *6-endo-trig* cyclization reaction of a γ-alkenyl ketone to produce a 3,4-dihydro-2*H*-pyran derivative (Scheme 1).

Pyrans and furans are important structural elements of many natural products[5] and pharmaceuticals[6] and valuable reaction precursors or intermediates in organic synthesis.[7] There are several synthetic strategies which yield pyrans and furans bearing different substitution patterns.[5,7,8] One frequently used method involves cyclization or cycloaddition reactions of unsaturated carbonyl compounds using transition metal catalysts[8e] such as Hg,[9] Au,[10] Pd,[11] Ag,[12] Co,[13] Zn,[14] Cu,[15] Rd,[16] and Pt[17] and other metals such as Ca,[18] Ga,[19] Sc,[20] and Bi.[21]

In 2008, Zhan and co-workers reported an interesting $FeCl_3$-catalyzed one-pot propargylation and cycloisomerization of 1,3-dicarbonyl compounds to form tetrasubstituted furans.[22] Other iron catalysts were also found to promote different synthetic approaches to furans and pyrans.[23] Schindler and co-workers subsequently identified $FeCl_3$ as an efficient Lewis acid-based catalyst for the formation of a range of 3,4-dihydro-2*H*-pyrans[24] and 3-carboxy-2,5-disubstituted furans.[25] This simple catalyst also proves to be an efficient promoter for the intramolecular carbonyl−olefin metathesis reaction in a series of elegant studies by the same group.[26] The similarity in catalytic activity between $FeCl_3$ and iodine, demonstrated by these studies and our earlier work (Scheme 1),[4] prompted us to investigate the possibility of using molecular iodine as a

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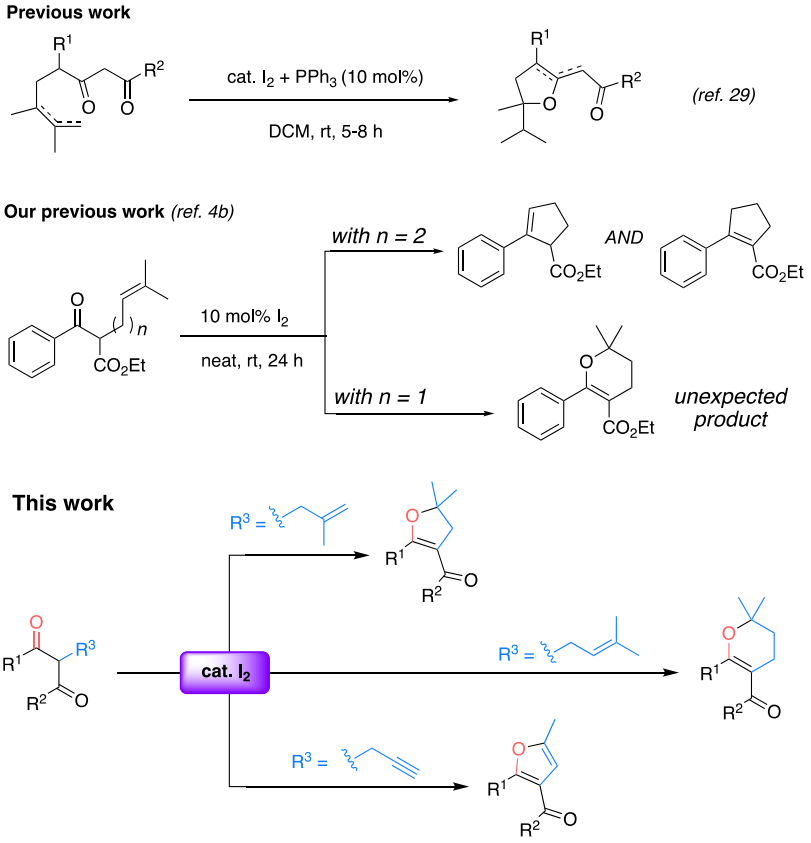
Scheme 1. Iodine-Catalyzed Reactions



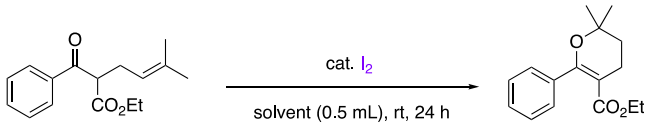
catalyst for the synthesis of a broader scope of pyrans and furans.

Molecular iodine has been frequently used to mediate the formation of heterocyclic compounds.[27] In the context of this work, I_2 has been used previously in super-stoichiometric amounts to obtain iodofurans via the iodoenoletherification of 2-alkenyl-substituted 1,3-dicarbonyl compounds or iodocyclization of vinyl acetate.[28] However, extraneous deiodination and acid-catalyzed isomerization reactions were required to obtain the non-iodinated furan products. Notably, an I_2-PPh_3 catalytic system was previously reported to promote the synthesis of furan-type spiro enol ether derivatives from unsaturated β-ketoesters.[29] However, these examples are scarce and non-systematic. Herein, we demonstrate that the I_2 catalyst can efficiently promote the cyclization of a broad range of α-allylated or α-propargylated carbonyl substrates to form a wide range of substituted pyrans and furans under mild reaction conditions with excellent outcomes.

PYRAN FORMATION REACTIONS

We started our investigation by optimizing the serendipitous reaction with substrate **1a** to form product **2a** (Table 1). The reaction generally consumed most of the starting material; however, the conversion to the cyclized product varied greatly with solvents (entries 1−10, Table 1). Reactions in acetonitrile or ethyl acetate (entries 5 and 7) seemed to give good conversion to the product but proceeded sluggishly. Alcoholic (MeOH and EtOH, entries 6 and 9) and ethereal solvents (THF and Et_2O, entries 4 and 8) showed consumption of **1a** without any noticeable formation of **2a**. In the cases of alcoholic solvents, we also observed some unwanted β-ester enol ethers.[30] A further investigation revealed that the majority of the product mixtures in these solvents contained unidentifiable oligomers of the starting material. Interestingly, further optimization studies (see page S2 in the experimental

Table 1. Optimization Studies[a]



1a **2a**

	mol % I_2	Solvents	conversion of **1a**[b]	yield **2a**
1	10	DCM	71%	21%
2	10	DCE	78%	20%
3	10	toluene	79%	8%
4	10	THF	87%	traces
5	10	MeCN	50%	48%
6	10	MeOH	89%	traces
7	10	EtOAc	62%	40%
8	10	Et_2O	91%	traces
9	10	EtOH	67%	traces
10	10	EtOH/H_2O (1:1)	86%	traces
11	10	Neat	100%	89%
12	5	Neat	94%	78%
13	2	Neat	63%	n.d.
14	1	Neat	48%	n.d.
15	0	Neat	0%	n.d.

[a]Reaction conditions: **1a** (0.5 mmol) and catalyst in the solvent at rt for 24 h. [b]Conversion determined by ^{1}H NMR using 1,3,5-triisopropylbenzene as an internal standard.

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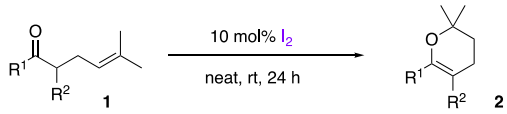
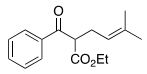
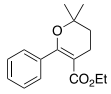
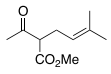
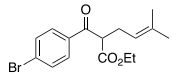
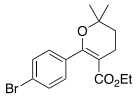
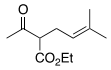
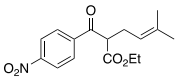
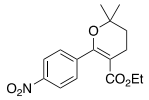
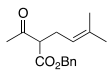
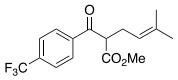
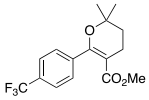
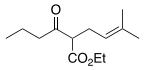
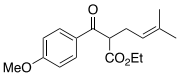
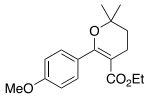
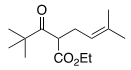
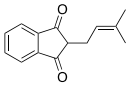
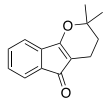
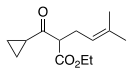
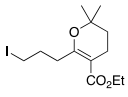
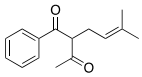
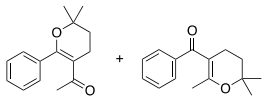
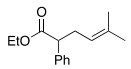
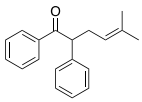
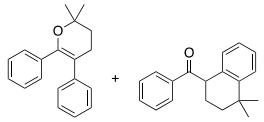
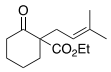
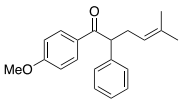
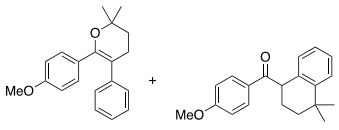
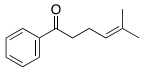
Table 2. Substrate Scope for 3,4-Dihydro-2*H*-pyrans[a]



substrates	products	substrates	products
 **1a**	 **2a**, 89%	 **1j**	 **2j**, 87%
 **1b**	 **2b**, 74%	 **1k**	 **2k**, 91%
 **1c**	 **2c**, 69%	 **1l**[c]	 **2l**, 51%
 **1d**	 **2d**, 73%	 **1m**	 **2m**, 68%
 **1e**	 **2e**, 38%	 **1n**	 **2n**, n.r.
 **1f**[c]	 **2f**, 82%	 **1o**[d]	 **2o'**, 15%
 **1g**[b,c]	 **2g**, 28% **2g'**, 44%	 **1p**	 **2p**, n.r.
 **1h**[c]	 **2h**, 80% **2h'**, 8%	 **1q**	 **2q**, n.r.
 **1i**	 **2i**, 20% *not found*	 **1r**	 **2r**, n.r.

[a]Reaction conditions: β-ketoester (0.5 mmol) and iodine (0.05 mmol) at rt for 24 h. [b]Same conditions but at 50 °C in a heating mantle. [c]Same conditions but with 20 mol % I_2. [d]0.5 mmol I_2 was used. See the experimental Supporting Information for more details.

Supporting Information for more details)[31] confirmed that the reactions, without a solvent under an ambient atmosphere and temperature, led to the formation of the target product in good to high yields (entries 11−15, Table 1). The optimal setup used 10 mol % I_2 catalyst to afford product **2a** in 89% yield (entry 11). It should be noted here that the reaction mixture was homogeneous under these conditions.

These optimal conditions were amenable to a range of other α-prenylated aryl ketones (Table 2) to form the corresponding 3,4-dihydro-2*H*-pyrans in good to excellent yields. The protocol tolerates a good range of functional groups, as expected from the benign nature of iodine. Interestingly, the reaction proceeded smoothly with electron-deficient aryl groups (**1b−d**, Table 2), while only low yield of the desired pyran product was observed with an electron-rich aryl group (**1e**, entry 5). It is possible that an electrophilic aromatic iodination side reaction rendered the iodine catalyst inactive, as we did observe some iodination to the aromatic ring on **1e**. With diketone **1g** (Table 2) where there are two carbonyl groups competing for the reaction, it was interesting to see that the cyclization preferred to occur on the aliphatic ketone. When there was an aryl group also at the α-position (**1h**), the

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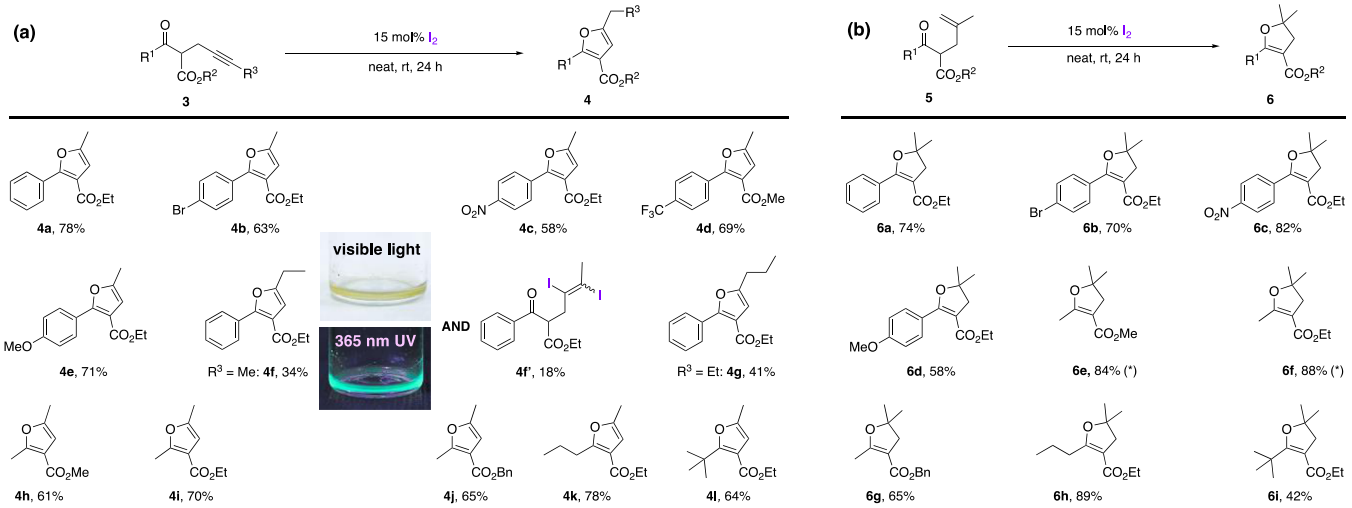
Scheme 2. Synthesis of (a) 3-Carboxy-2,5-disubstituted Furans and (b) 3-Carboxy-2,2,5-trisubstituted-4,5-dihydrofurans[a]



[a]Reaction conditions: **3** or **5** (0.5 mmol) and I_2 (0.075 mmol) stirred at rt for 24 h. (*) = yield determined by ^{1}H NMR using 1,3,5-triisopropylbenzene as an internal standard due to the volatility of the products, see the Supporting Information for more details.

reaction led to a mixture of the desired pyran **2h** (80%) and the tetrahydronaphthalene derivative **2h′** (8%) as the minor product. Compound **2h′** was presumably the outcome of the Friedel−Crafts-type alkylation reaction on the side-chain phenyl group, as was also previously observed with a $FeCl_3$ catalyst by the Schindler group.[26d] A prolonged reaction time of 48 h led to a product mixture of 62% **2h** and 16% **2h′**, suggesting that there might be an equilibrium converting **2h** to **2h′** via the reformation of **1h**.[26d] Substrate **1i** (Table 2), the *para*-methoxy derivative of **1h**, only led to poor yield of the cyclized product **2i**, and we were unable to identify the Friedel−Crafts byproduct **2i′** from this reaction.

Alkyl ketoester substrates also worked smoothly under our reaction conditions to form 3,4-dihydro-2*H*-pyran products in moderate to high yields (**2j−2m**, Table 2). However, no product formation was observed for the substrate with the *tert*-butyl substituent (**1n**, Table 2), presumably due to its steric hindrance. Surprisingly, the cyclopropyl group was not tolerated in this reaction setup, as some of substrate **1o** was converted to the ring-opened product **2o′**, which consumed the iodine catalyst. When we subjected **1o** to a stoichiometric amount of I_2, we were able to isolate **2o′** in 15% yield in addition to the recovered **1o** and some unidentified byproducts. The reaction did not take place on the ester carbonyl moiety of substrate **1p**. Furthermore, when we suppressed the substrates' tendency to tautomerize to their enol form, the reactivity was turned off, as demonstrated by substrates **1q** and **1r**. These negative outcomes provide insights into the mechanism of this iodine-catalyzed reaction (vide infra).

FURAN FORMATION REACTIONS

We then turned our attention to investigate the catalytic activity of I_2 in the synthesis of 3-carboxy-2,5-disubstituted furans from the α-propargyl-β-ketoester substrates (Scheme 2a). Similar optimization studies proved that 15 mol % iodine catalyst is the most efficient loading for this reaction.[31] The reaction worked relatively well on the 10 terminal alkyne substrates we studied (products **4a−e** and **4h−l**). Overall, yields were lower than those in the synthesis of pyrans in Table 1, most likely due to unwanted side reactions owing to the inherent reactivity of alkynes, as demonstrated later in the case of non-terminal alkyne substrate **3f** (product **4f**) especially. Notably, substrates with an electron-rich aryl group (**3e**) or bulky alkyl group (**3l**) still reacted to give the products in good yields. Given the poor reactivity of similar substrates (**1e** and **1m**) in Table 1, this is rather surprising. We suspect that the stability of the resulting aromatic furan systems gave sufficient driving force for the reactions to happen on **3e** and **3l**. Non-terminal alkyne substrates **3f** and **3g** also worked for this iodine-catalyzed 5-*exo* cyclization reaction to give the products, albeit in lower yields. A careful analysis of the reaction residue for substrate **3f** revealed adduct **4f′** as the major byproduct apart from the target **4f**. This unsurprising observation suggests that the addition of molecular iodine to the C−C multiple bond is always a competing process in our reactions. The affinity of I_2 to the C−C multiple bond, in addition to that of the carbonyl moiety, likely plays a role in the mechanism of this reaction, as discussed later in our computational studies.

Some members of this aryl-substituted furan family (**4a−4g**, Scheme 2a) exhibit strong luminescence in liquid forms. Photos of a representative sample of compound **4f** under visible light and 365 nm UV light were captured and are included in Scheme 2a to illustrate this phenomenon. Compound **4f** is pale yellow under visible light but becomes brightly green luminescent under 365 nm UV irradiation. This is interesting considering the simple structure of such a phenyl-furan system. Work to further advance the synthetic utility of this method to produce more interesting photoactive furan derivatives is ongoing in our laboratory and will be reported in due course.

Similar to reactions in Scheme 2a, the synthesis of 3-carboxy-2,2,5-trisubstituted-4,5-dihydrofurans from analogous alkenyl precursors also proceeded with good to excellent yields (Scheme 2b). Curiously, there was a decrease in yields, in comparison to other substrates, for the methoxyarene- and *tert*-butyl-containing products **6d** and **6i** (Scheme 2b), which is presumably related to the same trend in Table 1 where the cyclization did not lead to an aromatic system either. Overall, however, I_2 proves to be an efficient catalyst for the cyclization

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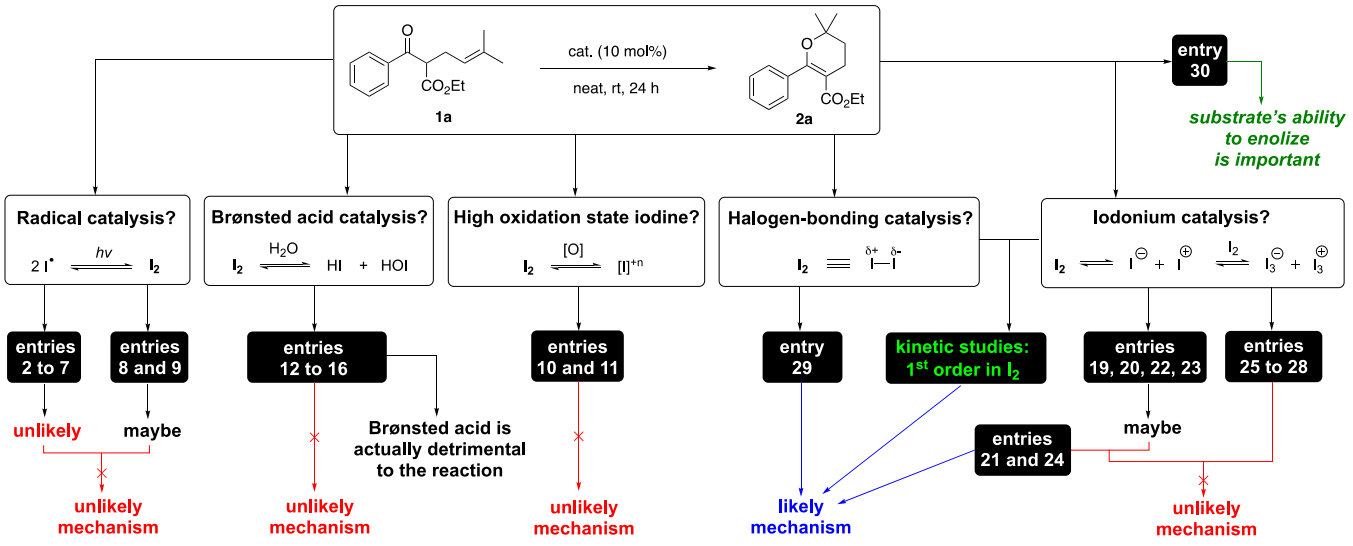
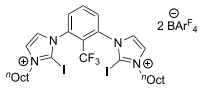
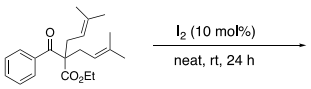
Table 3. Mechanistic Studies[a]



entry	cat. and conditions[b]	yield[c] (%)	entry	cat. and conditions[b]	yield[c] (%)
1	I_2 (ambient atmosphere, lab light)	89	17	KI (20 mol%)	n.r.
2	I_2 (ambient atmosphere, 365 nm)	messy reaction	18	I_2 (10 mol%) + KI (20 mol%)	16
3	I_2 (ambient atmosphere, blue LED)	36	19	NIS (reagent grade, 10 mol%)	38
4	I_2 (ambient atmosphere, green LED)	39	20	NIS (recryst., 10 mol%)	22
5	I_2 (ambient atmosphere, white LED)	82	21	NIS (recryst., 10 mol%) + KI (10 mol%)	69
6	I_2 (under argon, lab light)	80	22	ICl (reagent grade, 10 mol%)	31
7	I_2 (under argon, in the dark)	76	23	ICl (1.0 M in DCM, 10 mol%)	messy reaction
8	I_2 (10 mol%) + TEMPO (20 mol%)	messy reaction	24	ICl (liquid, 10 mol%) + KI (10 mol%)	58
9	I_2 (10 mol%) + BHT (20 mol%)	messy reaction	25	I_2 (10 mol%) + DMSO (20 mol%)	n.r.
10	I_2 (under O_2, lab light)	messy reaction	26	I_2 (10 mol%) + PPh_3 (10 mol%)	23
11	I_2 (10 mol%) + *m*CPBA (20 mol%)	messy reaction	27	I_2 (10 mol%) + NaOAc (20 mol%)	n.r.
12	I_2 (10 mol%) + water (20 mol%)	10	28	I_2 (10 mol%) + DABCO (20 mol%)	n.r.
13	I_2 (10 mol%) + TFA (10 mol%)	68	29	 (10 mol%)	51
14	I_2 (10 mol%) + TFA (20 mol%)	32			
15	TFA (10 mol%)	14			
16	HI (aq. 57% w/w, 10 mol%)	16	30	 1s instead of 1a (and also 1p-r - Table 2)	n.r.
	HI (gaseous, ~ 20 mol%)	messy reaction			
	HI (gaseous, ~ 100 mol%)	messy reaction			
	HI (MeCN solution, ~ 10 mol%)[d]	22			

[a]Reaction conditions: **1a** (0.2 mmol) and catalyst (0.02 mmol) at rt for 24 h. [b]Entries 1−10 used 10 mol % I_2; lab light means lighting conditions inside the fumehood (4 × 13 W fluorescent lights); entries 11−20 used in an ambient atmosphere and lab light again. [c]Yield of product **2a**; messy reaction means there were many unidentified products formed along with less than 10% conversion to **2a**; n.r. means that no conversion to product **2a** was observed. [d]HI in MeCN solution was prepared from freshly produced gaseous HI; the concentration was determined via titration; and the MeCN solvent volume was adjusted to 0.5 mL.

reaction of alkenyl or alkynyl carbonyl substrates to produce pyran and furan derivatives.

EXPERIMENTAL MECHANISTIC STUDIES

Based on our previous studies with iodine-catalyzed carbonyl−olefin metathesis reaction[4b,c] and common knowledge in the field, we suspected that this cyclization reaction could be catalyzed via one of some possible pathways such as halogen bonding, Brønsted acid, higher oxidation state iodine, iodonium ion, or free radical catalysis.[1d,32] We subsequently carried out a range of mechanistic studies to learn more about this system (Table 3). Radical generators such as TEMPO or radical traps such as BHT had diminishing effects on the catalytic activity of I_2 (entries 8−9). On the other hand, high-energy photoirradiation, with the intention to trigger iodine radical formation (entries 2−5, especially entry 4 where green light matched the homolytic cleavage energy of the I−I bond[33]), significantly reduced reaction efficiency. While these results seemed to contradict each other, we encountered several literature examples where TEMPO or BHT reacted directly with I_2 in a range of oxidation or substitution reactions,[34] which might interfere with our cyclization pathway. Moreover, it is also possible that BHT could trap the carbocation intermediate to form HI as well to further complicate the reaction. Thus, the negative outcomes from entries 8−9 should not be interpreted as the evidence for a radical mechanism of this reaction in particular; and TEMPO/BHT probably should not be used to study

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the mechanism of I_2-catalytic reactions in general. Collective information from entries 2−9 suggests that a radical pathway is mostly unlikely.

The reaction efficiency did not change much when we switched to an inert environment (Table 3, entries 6−7), but oxidative environments led to complicated reaction mixtures (entries 10−11). Therefore, any pathways involving higher oxidation states of iodine, including HOI, can be ruled out as unlikely. Spiking the reaction with water or a variation of Brønsted acids had a negative effect on the reaction outcomes (entries 12−16). The moderately successful reaction profiles in the presence of TFA as a co-catalyst or sole catalyst (entries 13−15) suggest that slightly acidic conditions might help the reaction but are not the determining factor. Most notably, the reaction performed in the presence of ∼10 mol % HI in acetonitrile solution instead of an I_2 catalyst led to much poorer yield of product **2a** (22%) than the results of entry 5 in Table 1 (48%). From these control experiments, it can be concluded that Brønsted acid catalysis was not the driving force for this reaction.

On the other hand, KI did not mediate the reaction by itself (entry 17) but actually suppressed the catalytic activity of I_2 (entry 18) instead. The positive but non-efficient outcomes of entries 19−20 and 22 with NIS and ICl, all favorable conditions for the formation of I^+ ions, indicate that iodonium can potentially activate the substrate for the reaction. However, further control reactions when NIS and ICl as I^+ sources were combined with KI as the I^- source (entries 21 and 24), which should generate I_2 *in situ*, led to better reaction outcomes than entries 19−20 and 22. These experiments hint that molecular iodine is more likely to be the reaction promoter than the iodonium ion. We also carried out a range of control experiments with some Brønsted/Lewis base additives (NaOAc, PPh_3, DMSO, DABCO, and entries 25−28 Table 3), which are capable of coordinating to the polarized iodine or iodonium ion. All of them led to negative results, partly supporting our hypothesis at this point that halogen bonding is the key element to promote the reaction. One of Huber's bidentate iodoazolium salt catalysts was moderately effective in promoting this reaction (entry 29), also supporting the halogen-bonding activation mode.[2]

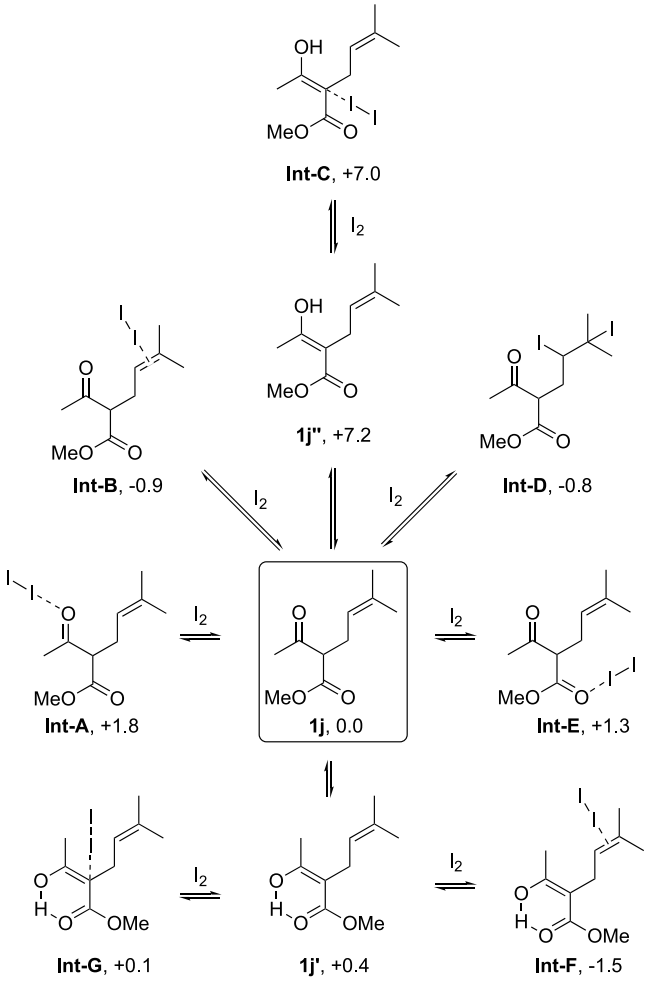
We subsequently carried out kinetic studies of the reaction with different catalyst loadings. The reaction order in the I_2 catalyst was determined to be the first order (see pages S3−S4 in the experimental Supporting Information for further details). This clearly ruled out the possibility of iodonium catalysis, as iodonium and its iodide counterion often associate with iodine molecules, leading to a higher empirical reaction order in I_2.[1d,32] All of these studies suggest that the reaction mechanism might involve the intact but polarized molecular iodine catalyst, activating the substrate through halogen-bonding interactions.

COMPUTATIONAL MECHANISTIC STUDIES

To be able to further elucidate the reaction mechanism, we subsequently evaluated several different reaction pathways using density functional theory (DFT) calculations. The geometry optimizations were performed with the PBE0 density functional,[35] in combination with the Def2TZVP basis set[36] for all atoms except iodine, for which Def2TZVP(D) and the corresponding ECP were used.[37] Grimme's D3 empirical dispersion with Becke-Johnson damping was applied.[38] The reactions were carried out under neat conditions, but to account for the overall effect of the reaction medium, the calculations were performed using SMD implicit solvation model for acetonitrile, which was also a working solvent for this reaction.[31] The recently corrected radius for the iodine atom for SMD calculations was used.[39] Substrate **1j** (R^1 = Me, R^2 = OMe) was selected for the study to reduce the degrees of freedom and simplify analysis. The yield of the reaction with this substrate was also representative of the general scope.

We first investigated the possible tautomers of **1j** and their coordinating adducts with molecular iodine (I_2), as depicted in Scheme 3.[40] As could be expected for a β-ketoester derivative,

Scheme 3. Possible 1j·I_2 Adducts (Free Energy Values Reported in kcal/mol)



the *Z* enol tautomer (**1j′**) is easily accessible at room temperature (ΔG = +0.4 kcal/mol). The *E* enol tautomer (**1j″**), while being much higher in energy, is still energetically accessible. All of the substrate·I_2-coordinating adducts are also accessible at room temperature, with a preference for the alkene·I_2 (**Int-B** and **Int-F**). The diiodination of the alkene (**Int-D**) is only slightly exergonic (ΔG = −0.8 kcal/mol) and thus reversible.

Interestingly, complexation of molecular iodine to the alkene moiety is even more favorable in the enol form than in the keto form (**Int-B** vs **Int-F**). Analysis of the structures of **Int-B** and **Int-F** suggests that this stabilization could be attributed to additional favorable electrostatic $O^{\delta-}\cdots I^{\delta+}$ interactions in **Int-F**, as depicted in Figure 1. We noticed a shortening of the enol-carbonyl hydrogen bond in **Int-G** (1.54 Å) with respect to that of **Int-F** (1.57 Å).[40] We postulated that the association of I_2 significantly increases O_{enol}−H acidity. Indeed, we also observed a H···alkene interaction in **Int-C** that would suggest that the enol proton could act as a strong acid.

With this assumption in mind, we investigated a mechanism in which this O_{enol}−H would be sufficiently *acidic* to protonate the alkene side chain and lead to the formation of a

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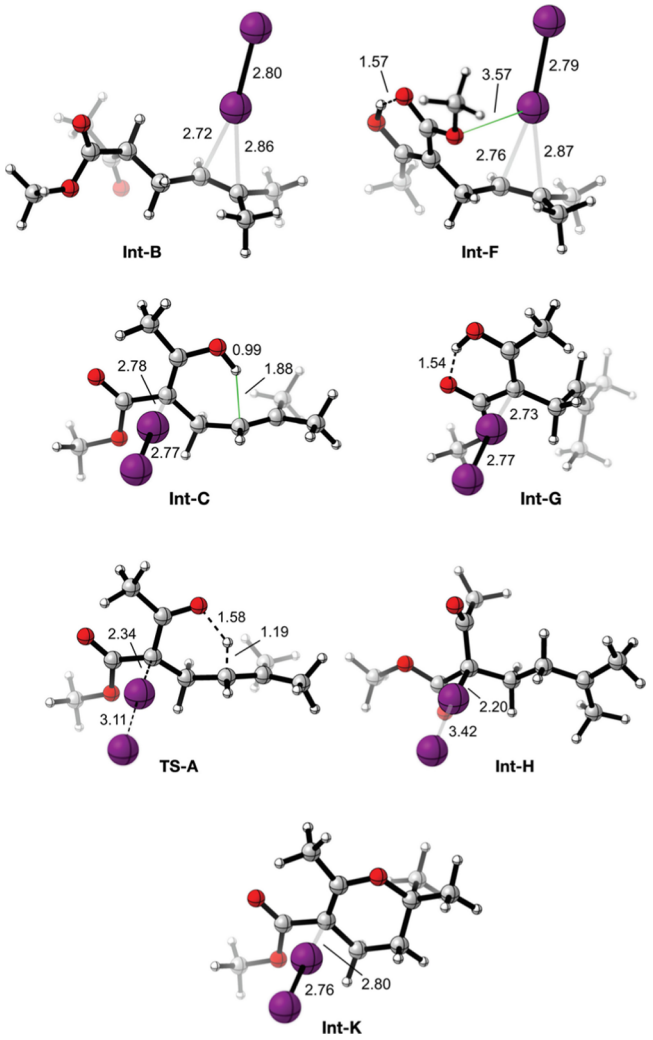
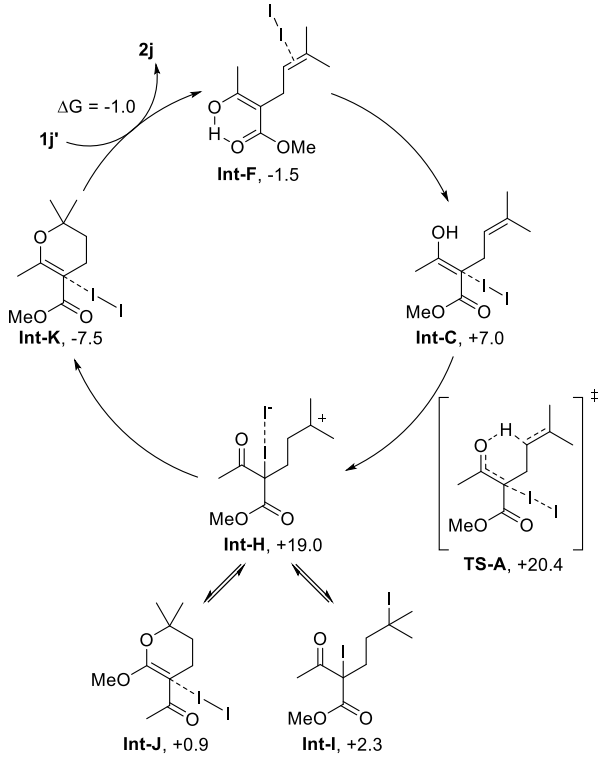


Figure 1. Structures of the selected intermediates and transition state in Schemes 3 and 4 (bond lengths in Å).

carbocationic intermediate that would ultimately lead to the desired product. It should be noted here that our control experiments with Brønsted acid or base additives in Table 3 collectively suggest the possibility of this enolization pathway. By taking away the enolization ability from the substrate (entry 30 Table 3), the reaction did not work at all, which further supports this hypothesis. The results of the calculations are illustrated in Scheme 4.

Gratifyingly, the transition state of intramolecular proton transfer (**TS-A**) did indeed prove to be reasonable ($\Delta G^{\ddagger}$ = 21.9 kcal/mol from **Int-F**). Through this process, the carbon−iodine bond shortens from 2.73 to 2.20 Å, indicating the formation of a covalent C−I bond. Accordingly, the iodine−iodine bond lengthens from 2.77 to 3.42 Å. With respect to the most stable substrate·I_2 adduct (**Int-F**), **TS-A** is considered to be the highest transition state in our postulated mechanism on the energy diagram, leading to the key carbocationic intermediate **Int-H**. In this context, the computed energetic span of the process (**Int-F**−**TS-A**, 21.9 kcal/mol) is in very good agreement (deviation below 1 kcal/mol) with the estimated experimental energetic span for substrate **1j**.[40] Furthermore, kinetic data are in accord with the kinetic model describing the proposed mechanism (page S15−S17 in the computational Supporting Information).[36]

Scheme 4. Plausible Catalytic Cycle Supported by DFT Calculations (Free Energies Reported in kcal/mol)



The resulting carbocationic intermediate (**Int-H**) is expected to react in mostly barrierless processes with the various nucleophilic sites on the intermediate, leading to three possible intermediates, **Int-I**, **Int-J**, and **Int-K**. Not surprisingly, all three pathways are found to be exergonic, but a deeper look into the thermodynamics provides interesting insights. Collapse of the iodide anion onto the carbocation is exergonic (−16.7 kcal/mol) and results in the formation of diiodoalkyl intermediate **Int-I**. Attack of the ester group on the carbocation, resulting in **Int-J**, is also exergonic by 18.1 kcal/mol. The alternative ester cyclization product formation is endergonic (+4.7 kcal/mol) with respect to the substrate and is thus thermodynamically disfavored.

While the formation of this product is kinetically possible under the reaction conditions, it is reversible, which explains why it is not observed. These two processes are expected to be reversible due to their respective exergonicities. In contrast, cyclization of **Int-H** by attack of the ketone oxygen atom is much more exergonic (−26.5 kcal/mol). Furthermore, the **Int-H** to **Int-K** process appears to be completely barrierless according to our exploration of the potential energy surface. It should be noted that no transition state for the S_N1-like S_N2 reaction of **Int-I** to form **Int-K** was found. The calculations thus support a S_N1 mechanism from **Int-H**.

Following cyclization, the I−I bond is regenerated in **Int-K**; the latter can be considered to be a **2j**·I_2 adduct. As a final step, to close the catalytic cycle, iodine must be transferred to a new substrate molecule. This step was found to be exergonic with respect to **1j′** (−1.0 kcal/mol) and **1j** (−0.6 kcal/mol). It can thus be concluded that there is no significant inhibition of the reaction by the product. Product **2j** is more stable by 6.5 kcal/mol with respect to substrate **1j**, confirming that the overall reaction is exergonic.

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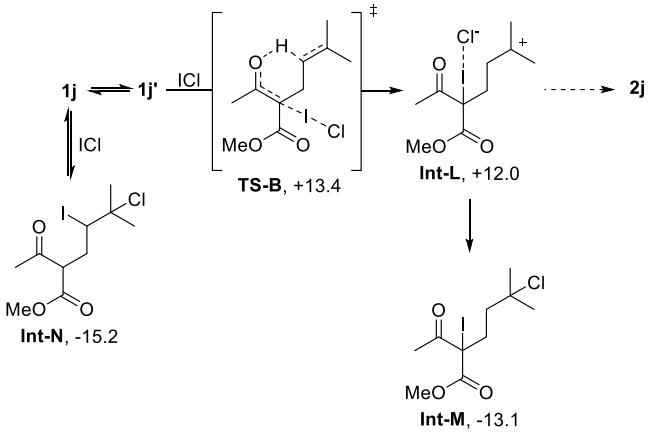
In this proposed mechanism, one could expect iodine monochloride to be an even better catalyst, as polarization along the I−Cl bond would make the iodine atom more Lewis acidic. However, what is observed experimentally is a significantly lower yield (31% vs 89% under otherwise identical conditions). We computed the H-transfer transition structure **TS-B**. As expected, with respect to **1j′** + ICl, we found it to be lower in free energy than the analogous **TS-A** (Scheme 5).

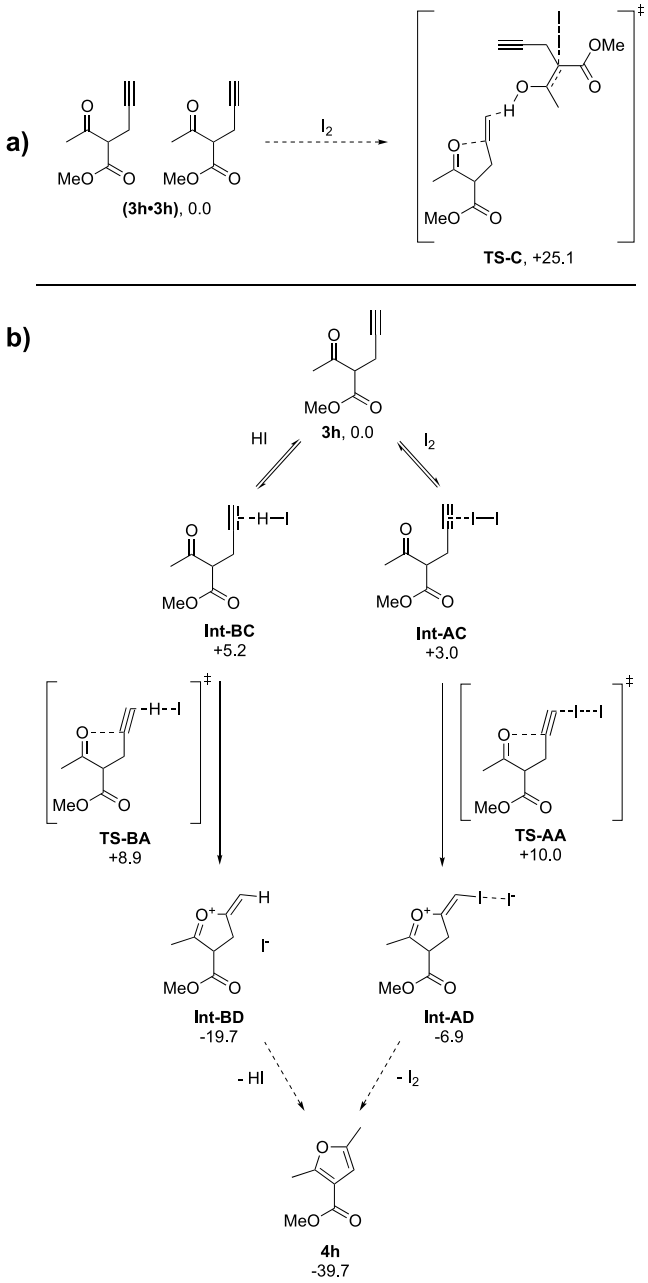
Scheme 5. Key Intermediates in the ICl-Catalyzed Reaction (Free Energies Reported in kcal/mol)



However, formation of **Int-M** from **Int-L** is much more exergonic (−25.1 kcal/mol) than the corresponding formation of **Int-I** from **Int-H**. This would result in a considerably slower reaction and thus lower yields in the same reaction time. Furthermore, the slower reaction/lower yield could also be explained by the exergonicity of formation of the iodochlorination intermediate **Int-N**. Interestingly, combination of catalytic iodine monochloride and potassium iodide results in a higher yield than iodine monochloride alone (Table 3, entry 24). One hypothesis is that iodine is formed *in situ* and acts as the active catalyst.

We then investigated the reaction of α-propargyl-β-ketoester substrates to form substituted furans using substrate **3h**. A mechanism analogous to the one in Scheme 4 would involve an alkenyl carbocation, which is unlikely. Accordingly, alternative pathways were considered. The key intermediates and transition structures are illustrated in Scheme 6.[40] First, we envisioned that two substrate molecules (**3h**·**3h**) could be involved in this process since the reaction is performed neat. The reaction could then proceed with this substrate pair via a concerted proton transfer and cyclization. The lowest-energy transition state found for this process (**TS-C**, Scheme 6a) is found to be at +25.1 kcal/mol with respect to **3h**·**3h**. This energy span is in good agreement with our observed reaction rates.[40] Alternatively, one could imagine an iodocyclization/protodeiodination mechanism, as reported for a different system by Saito and co-workers.[41] The key intermediates and transition structures provide facile reaction (Scheme 6b), with the highest barrier being +10.0 kcal/mol going from **3h** to **TS-AA**. However, this mechanism raises the possibility that HI could also be formed during the reaction, and an alternative HI-catalyzed process could also be involved. Consequently, we computed the key intermediates and transition structures for this pathway and found it to be even more favorable, with the highest activation barrier being +8.9 kcal/mol going from **3h** to

Scheme 6. Key Intermediates of the Considered Reaction Pathways of 3h (Free Energy Values Reported in kcal/mol)



TS-BA (Scheme 6b). To check the validity of this mechanistic hypothesis, we performed a test reaction of compound **3h** with 15 mol % HI and found that it provided 40% yield of the desired product within the same reaction time, compared with 61% yield when performed with the same catalyst loading of I_2. These results suggest that a much slower process may be limiting the rate of the HI-catalyzed reaction, which could be the proton-transfer steps. Due to their complex and uncertain nature, we did not compute these steps. However, we can conclude that the reaction involving α-propargyl-β-ketoester substrates is complicated and could involve parallel competing mechanisms.

In conclusion, we have developed a new practical protocol for the synthesis of 3,4-dihydro-2*H*-pyrans, 3-carboxy-2,2,5-trisubstituted-4,5-dihydrofurans, and 3-carboxy-2,5-disubstituted furans using molecular iodine as a catalyst under mild

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reaction conditions. The method tolerates a large range of functional groups and offers an easy, green alternative to currently available reaction protocols to access pyran and furan derivatives. A combination of experimental studies and DFT calculations revealed interesting mechanistic insights into this reaction. They strongly support that the association of iodine to the enol tautomer of the substrate enhances its acidity. This key intermediate is a sufficiently strong Brønsted acid to promote protonation of the alkene and formation of a key carbocation, from which only the formation of the desired product is thermodynamically favored.

EXPERIMENTAL SECTION

General Methods. Reactions, unless otherwise stated, were conducted under a positive pressure of argon in oven-dried glassware. Commercially available reagents were used as purchased unless otherwise noted. Analytical thin-layer chromatography was performed using aluminum plates precoated with silica gel 60 F254 (0.2 mm). Flash chromatography was performed using 230−400-mesh silica gel. Solvents used for chromatography are quoted as volume/volume ratios.

NMR spectroscopy was performed at 298 K using an AVANCE III HD 400 (400.1 MHz, ^{1}H; 100.6 MHz, ^{13}C; 376.5 MHz, ^{19}F), an AVANCE III 300 (300 MHz, ^{1}H; 75 MHz, ^{13}C; 282.5 MHz, ^{19}F) or an AVANCE III 400 (400.1 MHz, ^{1}H; 100.6 MHz, ^{13}C; 376.5 MHz, ^{19}F). Data are expressed in parts per million (ppm) downfield shift from tetramethylsilane with the residual solvent as an internal reference (δ 7.26 ppm for chloroform) and are reported as the position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (J in Hz), and integration (number of protons). ^{13}C NMR spectra were recorded at 298 K with complete proton decoupling. Data are expressed in parts per million (ppm) downfield shift relative to the internal reference (δ 77.2 ppm for the central peak of deuterated chloroform).

Infrared spectra were obtained on a Cary 630 FT-IR ATR spectrometer or a ThermoNicolet Avatar 370 FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). HRMS was performed at the Bioanalytical Mass Spectrometry Facility within the Mark Wainwright Analytical Centre at the University of New South Wales on an Orbitrap LTQ XL (Thermo Fisher Scientific, San Jose, CA, USA) ion trap mass spectrometer.

General Procedure for the Synthesis of Cyclization Precursors. Unless otherwise specified, the cyclization substrates were synthesized as follows: to a mixture of K_2CO_3 (5.5 mmol, 1.1 equiv) and KI (0.5 mmol, 0.1 equiv) in DMF (6 mL) was added the ketoester (5 mmol, 1.0 equiv) followed by dropwise addition of the alkyl bromide (6 mmol, 1.2 equiv). The reaction was left to stir at room temperature for 24−48 h. Water (10 mL) was subsequently added to the reaction mixture, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The crude material was then purified by flash column chromatography (silica gel) to provide the products.

General Procedure for I_2-Catalyzed Cyclization Reactions. To a 4 mL vial charged with an iodine catalyst (0.05 mmol, 10 mol % or 0.065 mmol, 15 mol %) and a stirrer bar was added starting material **1** or **3** or **5** (0.5 mmol). The vial was closed with a cap, and the mixture was stirred for 24 h at room temperature. The reaction mixture was then directly purified by flash column chromatography (silica gel) to provide the product **2** or **4** or **6**, respectively.

Characterization Data of Cyclization Precursors. *Ethyl 2-Benzoyl-5-methylhex-4-enoate (**1a**).*[42] The ketoester starting material (5.0 mmol, 1.0 equiv) was dissolved in THF (20 mL), and NaH (6.0 mmol, 1.2 equiv) was added slowly under N_2. After 15 min, a solution of 3,3-dimethylallyl bromide (6 mmol, 1.2 equiv) in THF (20 mL) was added under N_2. The reaction was left to stir at room temperature for 24 h. Water (10 mL) was added to the reaction mixture, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 50:1) provided 0.263 g of **1a** (10%) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03−7.95 (m, 2H), 7.62−7.54 (m, 1H), 7.52−7.41 (m, 2H), 5.16−5.06 (m, 1H), 4.29 (dd, J = 7.7, 6.9 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.80−2.57 (m, 2H), 1.65 (d, J = 1.3 Hz, 3H), 1.62 (d, J = 1.4 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H) ppm.

*Ethyl 2-(4-Bromobenzoyl)-5-methylhex-4-enoate (**1b**).*[24] The alkylation of the ketoester starting material was performed according to the general procedure on a 3.8 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 60:1) provided 0.51 g of **1b** (40%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88−7.80 (m, 2H), 7.65−7.57 (m, 2H), 5.08 (tp, J = 7.3, 1.4 Hz, 1H), 4.22 (t, J = 7.3 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.77−2.58 (m, 2H), 1.65 (d, J = 1.3 Hz, 3H), 1.62 (d, J = 1.3 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.2, 169.6, 135.2, 135.0, 132.2, 130.2, 128.9, 120.0, 61.6, 54.7, 27.8, 25.9, 17.9, 14.1 ppm.

*Ethyl 5-Methyl-2-(4-nitrobenzoyl)hex-4-enoate (**1c**).*[24] The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 20:1) provided 1.18 g of **1c** (77%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33−8.28 (m, 2H), 8.14−8.09 (m, 2H), 5.11−5.02 (m, 1H), 4.28 (t, J = 7.3 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.78−2.62 (m, 2H), 1.64 (q, J = 1.3 Hz, 3H), 1.61 (d, J = 1.3 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 193.9, 169.1, 150.5, 141.0, 135.4, 129.7, 124.0, 119.6, 61.8, 55.1, 27.6, 25.8, 17.9, 14.1 ppm.

*Methyl 5-Methyl-2-(4-(trifluoromethyl)benzoyl)hex-4-enoate (**1d**).* The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 20:1) provided 0.36 g of **1d** (23%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10−8.04 (m, J = 7.9, 0.9 Hz, 2H), 7.76−7.70 (m, 2H), 5.10−5.03 (m, 1H), 4.32 (t, J = 7.3 Hz, 1H), 3.67 (s, 3H), 2.78−2.63 (m, 2H), 1.63 (d, J = 1.3 Hz, 3H), 1.61 (d, J = 1.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.3, 169.8, 139.1, 135.3, 134.7 (q, J = 32.8 Hz), 129.0, 125.9 (q, J = 3.7 Hz), 123.6 (q, J = 272.5 Hz), 119.7, 54.6, 52.7, 27.8, 25.8, 17.8 ppm; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{16}H_{17}F_3O_3Na$, 337.1022; found, 337.1022; FTIR (neat): 2955, 1736, 1692, 1580, 1509, 1435, 1409, 1379 cm^{-1}.

*Ethyl 2-(4-Methoxybenzoyl)-5-methylhex-4-enoate (**1e**).* The ketoester starting material (2 mmol, 1.0 equiv) was slowly added to a flask containing NaH (5 mmol, 2.5 equiv) and THF (15 mL) under Ar. After 30 min, 3,3-dimethylallyl bromide (2 mmol, 1.0 equiv) was added, and the reaction left to stir at room temperature for 24 h. The reaction was cooled to 0 °C, and water (10 mL) was slowly added to the reaction mixture. The aqueous layer was extracted with DCM (3 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography and eluting with hexanes/EtOAc (90:10) provided 0.37 g of **1e** (63%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.95 (m, 2H), 6.97−6.91 (m, 2H), 5.14−5.05 (m, 1H), 4.24 (dd, J = 7.9, 6.7 Hz, 1H), 4.13 (qd, J = 7.1, 0.8 Hz, 2H), 3.87 (s, 3H), 2.77−2.57 (m, 2H), 1.65 (d, J = 1.3 Hz, 3H), 1.62 (d, J = 1.3 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 193.5, 170.1, 163.9, 134.6, 131.1, 129.5, 120.5, 114.0, 61.4, 55.6, 54.4, 27.9, 25.9, 17.9, 14.2 ppm; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{17}H_{22}O_4Na$, 313.1410; found, 313.1410; FTIR (neat): 2974, 2933, 2057, 1733, 1673, 1599, 1573, 1509, 1457, 1442, 1420, 1368 cm^{-1}.

*2-(3-Methylbut-2-en-1-yl)-1-phenylbutane-1,3-dione (**1g**).*[24] The alkylation of the diketone starting material was performed according to the general procedure on a 7.6 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1) provided 0.41 g of **1g** (23%) as a yellow oil. ^{1}H NMR (300 MHz,

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$CDCl_3$): δ 8.01−7.94 (m, 2H), 7.64−7.54 (m, 1H), 7.52−7.43 (m, 2H), 5.08−4.99 (m, 1H), 4.44 (t, J = 7.2 Hz, 1H), 2.68 (t, J = 7.2 Hz, 1H), 2.14 (s, 3H), 1.64 (d, J = 1.4 Hz, 3H), 1.61 (d, J = 1.2 Hz, 3H) ppm.

*5-Methyl-1,2-diphenylhex-4-en-1-one (**1h**).*[43] The ketoester starting material (5.0 mmol, 1.0 equiv) was dissolved in THF (20 mL), and NaH (6.0 mmol, 1.2 equiv) was added slowly under N_2. After 15 min, a solution of 3,3-dimethylallyl bromide (6 mmol, 1.2 equiv) in THF (20 mL) was added under N_2. The reaction was left to stir at room temperature for 24 h. Water (10 mL) was added to the reaction mixture, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. Purification by flash column chromatography and eluting with hexanes/EtOAc (75:1 to 60:1) gave 0.81 g of **1h** (60%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−8.00 (m, 2H), 7.50−7.44 (m, 1H), 7.43−7.35 (m, 4H), 7.35−7.29 (m, 2H), 7.25−7.19 (m, 1H), 5.14−5.01 (m, 1H), 4.63 (t, J = 7.3 Hz, 1H), 3.02−2.91 (m, 1H), 2.66−2.55 (m, 1H), 1.68 (d, J = 1.4 Hz, 3H), 1.61 (d, J = 1.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 199.7, 139.6, 136.9, 133.6, 132.7, 128.8, 128.7, 128.5, 128.2, 127.0, 121.6, 54.0, 32.8, 25.7, 17.7 ppm.

*1-(4-Methoxyphenyl)-5-methyl-2-phenylhex-4-en-1-one (**1i**).*[43] 4-Methoxydeoxybenzoin (2.6 mmol, 1.0 equiv) was added to a flask containing NaH (6.5 mmol, 2.5 equiv) and dry THF (20 mL) under Ar. After 15 min, 3,3-dimethylallyl bromide (2.7 mmol, 1.0 equiv) was added. The reaction was heated to reflux in a sand bath and left to stir for 24 h. The reaction was then cooled to 0 °C, and water (10 mL) was slowly added to the reaction mixture. The aqueous layer was extracted with DCM (3 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography and eluting with hexanes/EtOAc (80:20) provided 0.50 g of **1i** (65%) as a viscous light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99−7.90 (m, 2H), 7.34−7.24 (m, 4H), 7.22−7.16 (m, 1H), 6.90−6.82 (m, 2H), 5.02−5.10 (m, 1H), 4.49 (t, J = 7.3 Hz, 1H), 3.81 (s, 3H), 2.92−2.77 (m, 1H), 2.57−2.43 (m, 1H), 1.62 (d, J = 1.4 Hz, 3H), 1.54 (d, J = 1.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 198.4, 163.4, 140.1, 133.6, 131.1, 130.1, 128.9, 128.3, 127.0, 121.9, 113.8, 55.5, 53.8, 32.9, 25.9, 17.9 ppm.

*Methyl 2-Acetyl-5-methylhex-4-enoate (**1j**).*[24] The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (20:1) provided 0.59 g of **1j** (64%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05−4.92 (m, 1H), 3.70 (s, 3H), 3.43 (t, J = 7.5 Hz, 1H), 2.52 (t, J = 7.2 Hz, 2H), 2.20 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 203.1, 170.1, 135.0, 119.8, 59.7, 52.4, 29.2, 27.1, 25.8, 17.8 ppm.

*Ethyl 2-Acetyl-5-methylhex-4-enoate (**1k**).*[42] The alkylation of the ketoester starting material was performed according to the general procedure on a 7.6 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (20:1) provided 0.65 g of **1k** (43%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90−4.82 (m, 1H), 4.01 (q, J = 7.1 Hz, 2H), 3.27 (t, J = 7.5 Hz, 1H), 2.40−2.31 (m, 2H), 2.05 (s, 3H), 1.50 (d, J = 1.4 Hz, 3H), 1.46 (d, J = 1.4 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 202.6, 169.3, 134.3, 119.7, 60.9, 59.5, 28.7, 26.7, 25.4, 17.4, 13.8 ppm.

*Benzyl 2-Acetyl-5-methylhex-4-enoate (**1l**).*[24] The alkylation of the ketoester starting material was performed according to the general procedure on a 7.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1) provided 0.64 g of **1l** (36%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.27 (m, 5H), 5.16 (s, 2H), 5.05−4.96 (m, 1H), 3.48 (t, J = 7.5 Hz, 1H), 2.60−2.50 (m, 2H), 2.17 (s, 3H), 1.65 (d, J = 1.4 Hz, 3H), 1.60 (d, J = 1.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (76 MHz, $CDCl_3$): δ 202.9, 169.6, 135.5, 135.0, 128.7, 128.5, 128.4, 119.7, 67.1, 59.9, 29.2, 27.1, 25.8, 17.9 ppm.

*Ethyl 2-Butyryl-5-methylhex-4-enoate (**1m**).* The alkylation of the ketoester starting material was performed according to the general procedure on a 3.8 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (20:1) provided 0.29 g of **1m** (34%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (tdq, J = 7.3, 2.9, 1.3 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.37 (t, J = 7.5 Hz, 1H), 2.51−2.33 (m, 4H), 1.59 (d, J = 1.3 Hz, 3H), 1.55 (d, J = 1.4 Hz, 3H), 1.58−1.48 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 205.1, 169.6, 134.5, 120.0, 61.2, 59.0, 44.1, 27.0, 25.7, 17.7, 16.9, 14.1, 13.5 ppm; HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{22}O_3Na$, 249.1461; found, 249.1461; FTIR (neat): 2966, 2933, 2877, 1736, 1714, 1446, 1368 cm^{-1}.

*Ethyl 5-Methyl-2-pivaloylhex-4-enoate (**1n**).* The alkylation of the ketoester starting material was performed according to the general procedure on a 3.8 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 50:1) provided 0.13 g of **1n** (10%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.00 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.86 (t, J = 7.3 Hz, 1H), 2.57−2.39 (m, 2H), 1.63 (q, J = 1.2 Hz, 3H), 1.59 (d, J = 1.7 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 210.0, 169.6, 134.5, 120.6, 61.2, 52.7, 45.4, 28.8, 26.2, 25.8, 17.8, 14.1 ppm; HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{24}O_3Na$, 263.1618; found, 263.1618; FTIR (neat): 2970, 2933, 2873, 1736, 1703, 1476, 1464, 1368 cm^{-1}.

*Ethyl 2-(Cyclopropanecarbonyl)-5-methylhex-4-enoate (**1o**).*[24] The alkylation of the ketoester starting material was performed according to the general procedure on a 3.8 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 50:1) provided 0.3941 g of **1o** (46%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10−4.98 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.55 (t, J = 7.5 Hz, 1H), 2.68−2.49 (m, 2H), 2.13−1.99 (m, 1H), 1.67 (d, J = 1.3 Hz, 3H), 1.63 (d, J = 1.4 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.14−1.03 (m, 2H), 0.97−0.84 (m, 2H) ppm; ^{13}C{^{1}H} NMR (76 MHz, $CDCl_3$): δ 205.3, 169.9, 134.6, 120.1, 61.3, 60.2, 27.1, 25.9, 19.9, 17.9, 14.3, 11.9, 11.6 ppm.

*Ethyl 2-Benzoylpent-4-ynoate (**3a**).*[9] The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (20:1) provided 0.48 g of **3a** (42%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−8.01 (m, 2H), 7.64−7.58 (m, 1H), 7.53−7.46 (m, 2H), 4.57 (t, J = 7.4 Hz, 1H), 4.16 (qd, J = 7.1, 1.4 Hz, 2H), 2.90 (qdd, J = 17.0, 7.4, 2.7 Hz, 2H), 1.99 (t, J = 2.7 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 193.4, 168.3, 136.0, 133.9, 128.9, 128.8, 80.7, 70.5, 61.9, 53.3, 18.4, 14.0 ppm.

*Ethyl 2-(4-Bromobenzoyl)pent-4-ynoate (**3b**).*[44] The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:1) provided 0.35 g of **3b** (23%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 4.50 (t, J = 7.4 Hz, 1H), 4.16 (qd, J = 7.1, 1.3 Hz, 2H), 2.97−2.80 (m, 2H), 1.98 (t, J = 2.7 Hz, 1H), 1.18 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 192.5, 168.1, 134.8, 132.2, 130.5, 129.3, 80.5, 70.6, 62.1, 53.3, 18.4, 14.1 ppm.

*Ethyl 2-(4-Nitrobenzoyl)pent-4-ynoate (**3c**).*[45] The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:1) provided 0.69 g of **3c** (50%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37−8.32 (m, 2H), 8.22−8.17 (m, 2H), 4.57 (t, J = 7.4 Hz, 1H), 4.17 (qd, J = 7.1, 0.8 Hz, 2H), 2.93 (dt, J = 7.6, 2.6 Hz, 2H), 1.99 (s, 1H), 1.18 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 192.3, 167.5, 150.5, 140.4, 129.8, 123.9, 80.1, 70.8, 62.2, 53.4, 18.1, 13.9 ppm.

*Methyl 2-(4-(Trifluoromethyl)benzoyl)pent-4-ynoate (**3d**).* The alkylation of the ketoester starting material was performed according to the general procedure on a 5.1 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:1)

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provided 0.87 g of **3d** (62%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12−8.07 (m, 2H), 7.73−7.68 (m, 2H), 4.60 (t, J = 7.4 Hz, 1H), 3.64 (s, 3H), 2.93−2.78 (m, 2H), 1.96 (t, J = 2.6 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 192.6, 168.3, 138.6, 134.9 (q, J = 32.9 Hz), 129.2, 125.8 (q, J = 3.7 Hz), 123.4 (q, J = 272.4 Hz), 80.2, 70.7, 53.1, 52.9, 18.3 ppm; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{14}H_{11}F_3O_3Na$, 307.0552; found, 307.0552; FTIR (neat): 3290, 2959, 1740, 1692, 1580, 1513, 1435, 1409, 1319 cm^{-1}.

*Ethyl 2-(4-Methoxybenzoyl)pent-4-ynoate (**3e**).*[44] The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (10:1) provided 0.33 g of **3e** (26%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 4.45 (t, J = 7.4 Hz, 1H), 4.03 (qd, J = 7.1, 1.5 Hz, 2H), 3.74 (s, 3H), 2.86−2.65 (m, 2H), 1.92 (t, J = 2.7 Hz, 1H), 1.06 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 191.3, 168.2, 163.9, 131.0, 128.6, 113.7, 80.6, 70.2, 61.4, 55.3, 52.5, 18.1, 13.7 ppm.

*Ethyl 2-Benzoylhex-4-ynoate (**3f**).*[46] The ketoester precursor (2 mmol, 1.0 equiv) was slowly added to a flask containing NaH (5 mmol, 2.5 equiv) and dry THF (20 mL) under Ar. After 20 min, 1-bromo-2-propyne (2 mmol, 1.0 equiv) was added. The reaction was heated to reflux in a sand bath and left to stir for 24 h. The reaction was then cooled to 0 °C, and water (10 mL) was slowly added to the reaction mixture. The aqueous layer was extracted with DCM (3 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography and eluting with hexanes/DCM (70:30 to 30:70) provided 0.20 g of **3f** (41%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−8.00 (m, 2H), 7.63−7.56 (m, 1H), 7.53−7.45 (m, 2H), 4.51 (t, J = 7.4 Hz, 1H), 4.16 (qd, J = 7.2, 0.7 Hz, 2H), 2.83 (m, 2H), 1.70 (t, J = 2.5 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.0, 168.8, 136.2, 133.8, 129.0, 128.8, 78.0, 75.4, 61.8, 53.9, 18.9, 14.1, 3.6 ppm.

*Ethyl 2-Benzoylhept-4-ynoate (**3g**).*[45] The ketoester precursor (3 mmol, 1.0 equiv) was slowly added to a flask containing NaH (7.5 mmol, 2.5 equiv) and THF (15 mL). After 30 min, 1-bromo-2-pentyne (3 mmol, 1.0 equiv) was added, and the reaction was left to stir at room temperature for 24 h. The reaction was cooled to 0 °C, and water (10 mL) was slowly added to the reaction mixture. The aqueous layer was extracted with DCM (3 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography and eluting with hexanes/DCM (50:50 to 40:60) provided 0.39 g of **3g** (50%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.95 (m, 2H), 7.57−7.50 (m, 1H), 7.46−7.38 (m, 2H), 4.49 (t, J = 7.5 Hz, 1H), 4.18−4.01 (m, 2H), 2.89−2.68 (m, 2H), 2.06−1.94 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.0, 168.6, 136.2, 133.6, 128.8, 128.6, 83.9, 75.4, 61.5, 53.6, 18.8, 13.9, 13.9, 12.2 ppm.

*Methyl 2-Acetylpent-4-ynoate (**3h**).*[47] The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:3) provided 0.11 g of **3h** (10%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.71 (t, J = 7.5 Hz, 1H), 2.72 (ddd, J = 7.5, 2.7, 1.5 Hz, 2H), 2.30 (s, 3H), 2.00 (t, J = 2.7 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (76 MHz, $CDCl_3$): δ 201.1, 168.7, 80.4, 70.5, 58.2, 52.9, 29.8, 17.6 ppm.

*Ethyl 2-Acetylpent-4-ynoate (**3i**).*[48] The alkylation of the ketoester starting material was performed according to the general procedure on a 7.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (50:1 to 10:1) provided 0.40 g of **3i** (34%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23 (q, J = 7.0 Hz, 2H), 3.69 (t, J = 7.5 Hz, 1H), 2.72 (ddd, J = 7.5, 2.7, 1.4 Hz, 2H), 2.31 (s, 3H), 1.99 (t, J = 2.7 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (76 MHz, $CDCl_3$): δ 201.2, 168.2, 80.5, 70.4, 62.0, 58.4, 29.7, 17.6, 14.2 ppm.

*Benzyl 2-Acetylpent-4-ynoate (**3j**).* The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/EtOAc (10:1) provided 0.23 g of **3j** (19%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.29 (m, 5H), 5.20 (s, 2H), 3.74 (t, J = 7.5 Hz, 1H), 2.79−2.68 (m, 2H), 2.25 (s, 3H), 1.99 (t, J = 2.7 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 200.9, 168.0, 135.2, 128.8, 128.7, 128.5, 80.4, 70.5, 67.6, 58.3, 29.7, 17.5 ppm; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{14}H_{14}O_3Na$, 253.0835; found, 253.0835; FTIR (neat): 2978, 2933, 2875, 1742, 1701, 1482, 1460, 1372 cm^{-1}.

*Ethyl 3-Oxo-2-(prop-2-yn-1-yl)hexanoate (**3k**).*[49] The alkylation of the ketoester starting material was performed according to the general procedure on a 5 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1 to 10:1) provided 0.36 g of **3k** (36%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (qd, J = 7.1, 1.3 Hz, 2H), 3.69 (t, J = 7.5 Hz, 1H), 2.79−2.67 (m, 2H), 2.67−2.48 (m, 2H), 1.98 (t, J = 2.7 Hz, 1H), 1.64 (h, J = 7.3 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 203.4, 168.2, 80.6, 70.3, 61.8, 57.6, 44.6, 17.5, 16.9, 14.1, 13.6 ppm.

*Ethyl 2-Pivaloylpent-4-ynoate (**3l**).*[44] The alkylation of the ketoester starting material was performed according to the general procedure on a 5 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (50:1) provided 0.65 g of **3l** (53%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22−4.11 (m, 3H), 2.81−2.62 (m, 2H), 1.97 (t, J = 2.7 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.21 (s, 9H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 208.5, 168.1, 80.9, 70.2, 61.6, 51.3, 45.1, 26.2, 19.2, 14.0 ppm.

*Ethyl 2-Benzoyl-4-methylpent-4-enoate (**5a**).*[20] The alkylation of the ketoester starting material was performed according to the general procedure on a 3.8 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (40:1) provided 0.82 g of **5a** (88%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93−7.86 (m, 2H), 7.46−7.38 (m, 1H), 7.36−7.28 (m, 2H), 4.67−4.62 (m, 1H), 4.62−4.58 (m, 1H), 4.48 (dd, J = 8.0, 6.7 Hz, 1H), 3.98 (qd, J = 7.1, 1.0 Hz, 2H), 2.61 (qdd, J = 15.3, 7.5, 1.2 Hz, 2H), 1.62 (s, 3H), 1.00 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.1, 169.0, 141.8, 135.9, 133.2, 128.4, 128.3, 111.9, 60.9, 52.3, 36.2, 22.2, 13.6 ppm.

*Ethyl 2-(4-Bromobenzoyl)-4-methylpent-4-enoate (**5b**).* The alkylation of the ketoester starting material was performed according to the general procedure on a 3.8 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1) provided 0.36 g of **5b** (29%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.85 (m, 2H), 7.65−7.59 (m, 2H), 4.77 (qt, J = 1.5, 0.8 Hz, 1H), 4.69 (qd, J = 1.5, 1.0 Hz, 1H), 4.48 (dd, J = 7.8, 6.9 Hz, 1H), 4.13 (qd, J = 7.2, 0.8 Hz, 2H), 2.79−2.64 (m, 2H), 1.76 (d, J = 0.6 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 193.7, 169.3, 142.0, 135.1, 132.2, 130.3, 129.0, 112.4, 61.7, 52.9, 36.5, 22.8, 14.1 ppm; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{15}H_{17}{}^{79}BrO_3Na$, 347.0254 and $C_{15}H_{17}{}^{81}BrO_3Na$, 349.0233; found, 347.0256 and 349.0232; FTIR (neat): 3078, 2977, 2936, 1733, 1684, 1584, 1226 cm^{-1}.

*Ethyl 4-Methyl-2-(4-nitrobenzoyl)pent-4-enoate (**5c**).* The alkylation of the ketoester starting material was performed according to the general procedure on a 5.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1 to 20:1) provided 0.63 g of **5c** (43%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34−8.28 (m, 2H), 8.19−8.12 (m, 2H), 4.81−4.75 (m, 1H), 4.71−4.64 (m, 1H), 4.53 (t, J = 7.3 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.84−2.66 (m, 2H), 1.75 (t, J = 1.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 193.4, 168.9, 150.6, 141.7, 140.9, 129.7, 124.1, 112.7, 62.0, 53.4, 36.4, 22.7, 14.1 ppm; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{15}H_{17}NO_5Na$, 314.0999; found, 314.0996; FTIR (neat): 3112, 3082, 3052, 2970, 2936, 2873, 1718, 1692, 1647, 1602, 1524 cm^{-1}.

*Ethyl 2-(4-Methoxybenzoyl)-4-methylpent-4-enoate (**5d**).* The alkylation of the ketoester starting material was performed according

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to the general procedure on a 3.8 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1) provided 0.17 g of **5d** (16%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04−7.98 (m, 2H), 6.98−6.92 (m, 2H), 4.77 (s, 1H), 4.71 (s, 1H), 4.50 (dd, J = 8.1, 6.5 Hz, 1H), 4.13 (qd, J = 7.1, 1.3 Hz, 2H), 3.88 (s, 3H), 2.82−2.63 (m, 2H), 1.76 (dd, J = 1.4, 0.8 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 193.1, 169.9, 164.0, 142.4, 131.2, 129.3, 114.1, 112.2, 61.5, 55.7, 52.6, 36.7, 22.8, 14.2 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{20}O_4Na$, 299.1254; found, 299.1255; FTIR (neat): 3078, 2977, 2936, 2131, 1733, 1684, 1651, 1584 cm^{-1}.

*Methyl 2-Acetyl-4-methylpent-4-enoate (**5e**).*[50] The alkylation of the ketoester starting material was performed according to the general procedure on a 7.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1) provided 0.48 g of **5e** (40%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.79 (s, 1H), 4.69 (s, 1H), 3.73 (s, 3H), 3.69 (t, J = 7.6 Hz, 1H), 2.64−2.50 (m, 2H), 2.24 (s, 3H), 1.73 (t, J = 1.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 202.5, 170.0, 141.9, 112.3, 58.1, 52.5, 35.9, 28.9, 22.4 ppm.

*Ethyl 2-Acetyl-4-methylpent-4-enoate (**5f**).*[51] The alkylation of the ketoester starting material was performed according to the general procedure on a 7.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:1) provided 0.81 g of **5f** (63%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.57 (s, 1H), 4.49 (s, 1H), 3.98 (q, J = 7.1 Hz, 2H), 3.49 (t, J = 7.6 Hz, 1H), 2.35 (d, J = 7.6 Hz, 2H), 2.03 (s, 3H), 1.53 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.9, 169.0, 141.6, 111.8, 60.9, 57.8, 35.5, 28.4, 22.0, 13.7 ppm.

*Benzyl 2-Acetyl-4-methylpent-4-enoate (**5g**).*[20] The alkylation of the ketoester starting material was performed according to the general procedure on a 7 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1) provided 1.06 g of **5g** (62%) as a light-yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31−7.19 (m, 5H), 5.08 (s, 2H), 4.70 (s, 1H), 4.62 (s, 1H), 3.68 (dd, J = 8.0, 7.2 Hz, 1H), 2.59−2.45 (m, 2H), 2.09 (s, 3H), 1.64 (t, J = 1.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.7, 168.9, 141.5, 135.2, 128.3, 128.1, 128.0, 112.0, 66.7, 57.8, 35.5, 28.4, 22.0 ppm.

*Ethyl 2-(2-Methylallyl)-3-oxohexanoate (**5h**).*[51] The alkylation of the ketoester starting material was performed according to the general procedure on a 7.0 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1 to 50:1) provided 0.37 g of **5h** (25%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.70 (s, 1H), 4.61 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 7.6 Hz, 1H), 2.56−2.33 (m, 4H), 1.66 (s, 3H), 1.54 (h, J = 7.3 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 204.5, 169.4, 142.0, 112.1, 61.3, 57.5, 43.7, 35.7, 22.4, 16.8, 14.1, 13.5 ppm.

*Ethyl 4-Methyl-2-pivaloylpent-4-enoate (**5i**).*[20] The alkylation of the ketoester starting material was performed according to the general procedure on a 3.8 mmol scale. Purification by flash column chromatography and eluting with hexanes/Et_2O (50:1) provided 0.58 g of **5i** (68%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.75 (s, 1H), 4.69 (s, 1H), 4.17−4.06 (m, 3H), 2.65−2.53 (m, 1H), 2.46−2.34 (m, 1H), 1.73 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.16 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 209.4, 169.4, 142.2, 112.7, 61.4, 51.3, 45.5, 37.5, 26.3, 22.6, 14.2 ppm.

Characterization Data of Cyclized Products. *Ethyl 2,2-Dimethyl-6-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (**2a**).*[24] The cyclization of **1a** was performed on a 1 mmol scale with 10 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 50:1) provided 231 mg of **2a** (89%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.37−7.27 (m, 5H), 3.92 (q, J = 7.1 Hz, 2H), 2.49 (t, J = 6.7 Hz, 2H), 1.76 (t, J = 6.7 Hz, 2H), 1.36 (s, 6H), 0.91 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (76 MHz, $CDCl_3$): δ 168.9, 162.2, 137.9, 128.7, 128.6, 127.7, 102.0, 76.3, 59.8, 32.4, 26.5, 20.4, 13.8 ppm.

*Ethyl 6-(4-Bromophenyl)-2,2-dimethyl-3,4-dihydro-2H-pyran-5-carboxylate (**2b**).*[24] The cyclization of **1b** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 50:1) provided 51.4 mg of **2b** (74%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.43 (m, 2H), 7.21−7.16 (m, 2H), 3.95 (q, J = 7.1 Hz, 2H), 2.47 (t, J = 6.7 Hz, 2H), 1.75 (t, J = 6.7 Hz, 2H), 1.35 (s, 6H), 0.99 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (76 MHz, $CDCl_3$): δ 168.5, 161.1, 136.7, 130.9, 130.4, 123.0, 102.5, 76.6, 59.9, 32.3, 26.5, 20.3, 14.0 ppm.

*Ethyl 2,2-Dimethyl-6-(4-nitrophenyl)-3,4-dihydro-2H-pyran-5-carboxylate (**2c**).*[24] The cyclization of **1c** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at room temperature. As the starting material was solid, two drops of DCE were added to aid mixing. Purification by flash column chromatography and eluting with hexanes/EtOAc (20:1) provided 105 mg of **2c** (69%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.21−8.16 (m, 2H), 7.49−7.42 (m, 2H), 3.94 (q, J = 7.1 Hz, 2H), 2.50 (t, J = 6.7 Hz, 2H), 1.77 (t, J = 6.7 Hz, 2H), 1.36 (s, 6H), 0.98 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.7, 159.8, 147.8, 144.3, 129.7, 122.9, 103.6, 77.1, 60.1, 32.1, 26.4, 20.1, 13.9 ppm.

*Methyl 2,2-Dimethyl-6-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-pyran-5-carboxylate (**2d**).* The cyclization of **1d** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 20:1) provided 120.3 mg of **2d** (73%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 3.50 (s, 3H), 2.51 (t, J = 6.7 Hz, 2H), 1.78 (t, J = 6.7 Hz, 2H), 1.37 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.50, 161.06, 141.20 (d, J = 1.5 Hz), 130.66 (q, J = 32.4 Hz), 129.04, 124.75 (q, J = 3.8 Hz), 124.20 (q, J = 272.2 Hz), 102.60, 76.87, 51.17, 32.20, 26.40, 20.22 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{17}F_3O_3Na$, 337.1022; found, 337.1023; FTIR (neat): 2977, 2948, 2854, 1714, 1695, 1632, 1610, 1323, 1297 cm^{-1}.

*Ethyl 6-(4-Methoxyphenyl)-2,2-dimethyl-3,4-dihydro-2H-pyran-5-carboxylate (**2e**).* The cyclization of **1e** was performed on a 1 mmol scale with 10 mol % I_2 in 24 h at room temperature. As the product has the same R_f as that of the starting material and could not be separated in all eluent systems attempted (hexanes/EtOAc, hexanes/DCM, and hexanes/Et_2O), the reaction yield was determined to be approximately 38% from a combination of column fractions via ^1H NMR, using 1,3,5-triisopropylbenzene as an internal standard. To allow characterization of the product, a small amount of the almost pure compound **2e** was able to be obtained after column chromatography with hexanes/DCM (10:90); however, a trace amount of the uncyclized starting material (compound **1e**) is still visible in the spectra. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29−7.23 (m, 2H), 6.88−6.82 (m, 2H), 3.96 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 2.48 (t, J = 6.8 Hz, 2H), 1.74 (t, J = 6.8 Hz, 2H), 1.35 (s, 6H), 1.00 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 169.0, 161.9, 160.2, 130.2, 130.1, 113.1, 101.4, 76.2, 59.8, 55.4, 32.4, 26.5, 20.5, 14.1 ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}O_4$, 291.1591; found, 291.1589; FTIR (neat): 2976, 2934, 1681, 1603, 1509, 1459, 1369, 1295, 1245 cm^{-1}.

*2,2-Dimethyl-3,4-dihydroindeno[1,2-b]pyran-5(2H)-one (**2f**).*[52] The cyclization of **1f** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at 50 °C in a heating mantle. Purification by flash column chromatography and eluting with hexanes/EtOAc (50:1 to 25:1) provided 87.7 mg of **2f** (82%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38−7.32 (m, 1H), 7.30−7.16 (m, 2H), 7.10−7.04 (m, 1H), 2.30 (t, J = 6.4 Hz, 2H), 1.76 (t, J = 6.4 Hz, 2H), 1.42 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (76 MHz, $CDCl_3$): δ 193.4, 173.8, 138.6, 133.9, 131.8, 129.7, 120.8, 117.5, 106.4, 81.1, 32.7, 26.7, 14.4 ppm.

*1-(2,2-Dimethyl-6-phenyl-3,4-dihydro-2H-pyran-5-yl)ethan-1-one (**2g**) and Phenyl(2,2,6-trimethyl-3,4-dihydro-2H-pyran-5-yl)-methanone (**2g′**).*[24] The cyclization of **1g** was performed on a 1 mmol scale with 15 mol % I_2 in 24 h at 50 °C in a heating mantle. Purification by flash column chromatography and eluting with hexanes/EtOAc (75:1) provided 64 mg of **2g** (26%) and 102 mg of **2g′** (44%) as light-yellow oils. **2g**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.44−7.32 (m, 5H), 2.48 (t, J = 6.8 Hz, 2H), 1.74 (t, J = 6.8 Hz, 2H), 1.67 (s, 3H), 1.36 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (76 MHz, $CDCl_3$): δ

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200.5, 163.5, 137.6, 129.9, 129.4, 128.5, 114.1, 76.6, 32.5, 30.6, 26.3, 20.2 ppm. **2g′**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66−7.60 (m, 2H), 7.51−7.35 (m, 3H), 2.39 (tt, J = 6.6, 1.5 Hz, 2H), 1.73 (t, J = 1.5 Hz, 3H), 1.68 (t, J = 6.6 Hz, 2H), 1.33 (s, 6H) ppm; ^{13}C NMR (76 MHz, $CDCl_3$): δ 198.8, 160.7, 141.2, 131.5, 128.5, 128.5, 108.9, 75.5, 32.5, 26.8, 21.3, 21.2 ppm.

*2,2-Dimethyl-5,6-diphenyl-3,4-dihydro-2H-pyran (**2h**) and (4,4-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)(phenyl)methanone (**2h′**).*[26d] The cyclization of **1h** was performed on a 1 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (75:1 to 50:1) provided 208.0 mg of **2h** (80%) and 21.0 mg of **2h′** (8%) as yellow oils. **2h**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22−7.04 (m, 10H), 2.50 (t, J = 6.8 Hz, 2H), 1.88 (t, J = 6.8 Hz, 2H), 1.42 (s, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 148.0, 142.2, 137.4, 130.4, 129.7, 129.6, 128.8, 128.2, 128.1, 128.0, 127.6, 127.5, 127.3, 127.2, 125.7, 110.4, 73.7, 33.8, 26.5, 25.9 ppm. **2h′**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07−7.99 (m, 2H), 7.64−7.55 (m, 1H), 7.55−7.47 (m, 2H), 7.47−7.41 (m, 1H), 7.30−7.20 (m, 1H), 7.14−7.03 (m, 1H), 6.96−6.87 (m, 1H), 4.84 (t, J = 6.4 Hz, 1H), 2.28−2.05 (m, 2H), 1.89−1.76 (m, 1H), 1.72−1.60 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H) ppm; ^{13}C{^{1}H} NMR (76 MHz, $CDCl_3$): δ 202.5, 146.5, 136.7, 133.8, 133.1, 129.4, 128.8, 128.8, 127.1, 126.9, 125.7, 48.4, 36.1, 33.8, 31.9, 31.6, 24.0 ppm.

*6-(4-Methoxyphenyl)-2,2-dimethyl-5-phenyl-3,4-dihydro-2H-pyran (**2i**).* The cyclization of **1i** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/DCM (60:40) provided 34.3 mg of **2i** (20%) as a yellow oil. The Friedel−Crafts-type byproduct **2i′** was not identified from the reaction mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22−7.02 (m, 7H), 6.73−6.61 (m, 2H), 3.73 (s, 3H), 2.48 (t, J = 6.8 Hz, 2H), 1.87 (t, J = 6.8 Hz, 2H), 1.41 (s, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.9, 147.7, 142.5, 130.8, 129.9, 129.7, 128.1, 125.5, 113.1, 109.3, 73.6, 55.3, 33.8, 26.5, 25.9 ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{23}O_2$, 295.1693; found, 295.1693; FTIR (neat): 2971, 2930, 2838, 1672, 1601, 1510, 1248 cm^{-1}.

*Methyl 2,2,6-Trimethyl-3,4-dihydro-2H-pyran-5-carboxylate (**2j**).*[24] The cyclization of **1j** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at room temperature. Because **2j** is quite volatile, the yield of this reaction was determined to be 87% by ^{1}H NMR using 1,3,5-triisopropylbenzene as an internal standard. Purification by flash column chromatography and eluting with hexanes/EtOAc (40:1) provided **2j** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H), 2.28 (td, J = 6.7, 1.5 Hz, 2H), 2.19 (t, J = 1.5 Hz, 3H), 1.59 (t, J = 6.7 Hz, 2H), 1.22 (s, 6H) ppm; ^{13}C{^{1}H} NMR (76 MHz, $CDCl_3$): δ 169.3, 164.1, 99.3, 75.6, 51.0, 32.4, 26.6, 20.9, 19.5 ppm.

*Ethyl 2,2,6-Trimethyl-3,4-dihydro-2H-pyran-5-carboxylate (**2k**).*[29] The cyclization of **1k** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at room temperature. Because **2k** is quite volatile, the yield of this reaction was determined to be 91% by ^{1}H NMR using 1,3,5-triisopropylbenzene as an internal standard. Purification by flash column chromatography and eluting with hexanes/EtOAc (40:1) provided **2k** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (q, J = 7.1 Hz, 2H), 2.33−2.25 (m, 2H), 2.20 (t, J = 1.5 Hz, 3H), 1.59 (t, J = 6.7 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.23 (s, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.9, 163.8, 99.5, 75.5, 59.6, 32.4, 26.6, 20.9, 19.6, 14.6 ppm.

*Benzyl 2,2,6-Trimethyl-3,4-dihydro-2H-pyran-5-carboxylate (**2l**).*[24] The cyclization of **1l** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (50:1 to 25:1) provided 71 mg of **2l** (51%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.27 (m, 5H), 5.16 (s, 2H), 2.36 (tq, J = 6.7, 1.5 Hz, 2H), 2.24 (q, J = 1.5 Hz, 3H), 1.62 (t, J = 6.7 Hz, 2H), 1.25 (s, 6H) ppm; ^{13}C{^{1}H} NMR (76 MHz, $CDCl_3$): δ 168.6, 164.6, 137.1, 128.6, 128.0, 127.9, 99.2, 75.7, 65.5, 32.4, 26.7, 21.0, 19.6 ppm.

*Ethyl 2,2-Dimethyl-6-propyl-3,4-dihydro-2H-pyran-5-carboxylate (**2m**).* The cyclization of **1m** was performed on a 0.2 mmol scale with 10 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 50:1) provided 32 mg of **2m** (68%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (q, J = 7.1 Hz, 2H), 2.59 (ddt, J = 8.7, 6.8, 0.9 Hz, 2H), 2.30 (tt, J = 6.7, 0.9 Hz, 2H), 1.59 (t, J = 6.7 Hz, 2H), 1.57−1.50 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.23 (s, 6H), 0.92 (t, J = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.8, 167.4, 99.3, 75.1, 59.6, 35.5, 32.4, 26.6, 21.3, 19.7, 14.5, 14.1 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{13}H_{22}O_3Na$, 249.1461; found, 249.1462; FTIR (neat): 2974, 2933, 2873, 1703, 1610, 1453, 1368, 1289 cm^{-1}.

*Ethyl 6-(3-Iodopropyl)-2,2-dimethyl-3,4-dihydro-2H-pyran-5-carboxylate (**2o′**).* The reaction of **1o** with the catalytic amount of I_2 did not lead to any significant amounts of identifiable products. Once the reaction was performed on a 0.5 mmol scale with the stoichiometric amount of I_2, it was possible to isolate some products from the reaction mixture. Purification by flash column chromatography and eluting with hexanes/DCM (50:50) provided 26 mg of **2o′** (15%) as a brown oil along with some other unidentifiable products. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, J = 7.1 Hz, 2H), 3.19 (t, J = 7.4 Hz, 2H), 2.71 (ddt, J = 8.5, 6.3, 0.9 Hz, 2H), 2.30 (tt, J = 6.7, 0.9 Hz, 2H), 2.08 (p, J = 7.4 Hz, 2H), 1.60 (t, J = 6.7 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.23 (s, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.5, 165.2, 100.2, 75.5, 59.8, 34.6, 32.3, 32.1, 26.6, 19.7, 14.6, 6.0 ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{22}IO_3$, 353.0609; found, 353.0605 (minor ∼15%); FTIR (neat): 2975, 2936, 1699, 1610, 1448, 1367, 1274, 1226 cm^{-1}.

*Ethyl 5-Methyl-2-phenylfuran-3-carboxylate (**4a**).*[9] The cyclization of **3a** was performed on a 0.5 mmol scale with 10 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/Et_2O (50:1 to 20:1) provided 102 mg of **4a** (78%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99−7.93 (m, 2H), 7.45−7.33 (m, 3H), 6.44 (q, J = 1.0 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.35 (d, J = 1.0 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.9, 156.1, 151.2, 130.2, 129.0, 128.3, 128.1, 114.6, 108.9, 60.5, 14.4, 13.5 ppm.

*Ethyl 2-(4-Bromophenyl)-5-methylfuran-3-carboxylate (**4b**).*[44] The cyclization of **3b** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:1) provided 110 mg of **4b** (63%) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 6.43 (q, J = 1.1 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.34 (d, J = 1.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.7, 154.8, 151.5, 131.3, 129.7, 129.0, 123.2, 115.1, 109.1, 60.6, 14.4, 13.4 ppm.

*Ethyl 5-Methyl-2-(4-nitrophenyl)furan-3-carboxylate (**4c**).*[53] The cyclization of **3c** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (20:1) provided 86 mg of **4c** (58%) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28−8.19 (m, 4H), 6.51 (d, J = 1.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.39 (d, J = 1.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.4, 153.1, 152.8, 147.4, 135.8, 128.5, 123.5, 117.7, 110.0, 61.0, 14.3, 13.5 ppm.

*Methyl 5-Methyl-2-(4-(trifluoromethyl)phenyl)furan-3-carboxylate (**4d**).* The cyclization of **3d** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1) provided 98 mg of **4d** (69%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 6.46 (q, J = 1.0 Hz, 1H), 3.83 (s, 3H), 2.37 (d, J = 1.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.1, 154.3, 152.3, 133.3, 130.5 (q, J = 32 Hz), 128.3, 125.2 (q, J = 3.8 Hz), 124.2 (q, J = 271.4 Hz), 115.8, 109.3, 51.8, 13.5 ppm; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −62.8 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{11}F_3O_3Na$, 307.0553; found, 307.0553; FTIR (neat): 2955, 1722, 1688, 1610, 1558, 1323, 1274 cm^{-1}.

*Ethyl 2-(4-Methoxyphenyl)-5-methylfuran-3-carboxylate (**4e**).* The cyclization of **3e** was performed on a 0.5 mmol scale with 15

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mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (50:1 to 20:1) provided 104 mg of **4e** (71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97−7.91 (m, 2H), 6.97−6.90 (m, 2H), 6.41 (q, J = 1.1 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 2.33 (d, J = 1.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.0, 160.2, 156.3, 150.4, 129.8, 122.9, 113.5, 113.3, 108.7, 60.3, 55.4, 14.4, 13.4 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{16}O_4Na$, 283.0941; found, 283.0942; FTIR (neat): 2977, 2929, 2836, 1710, 1606, 1502, 1252 cm^{-1}.

*Ethyl 5-Ethyl-2-phenylfuran-3-carboxylate (**4f**) and **4f′** Adduct.* The cyclization of **3f** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/DCM (1:1) provided 42 mg of **4f** (34%) as a colorless oil. Another byproduct (**4f′**) was also isolated from the reaction mixture in ∼18% yield, which was most likely the adduct of iodine to **3f**. **4f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−7.93 (m, 2H), 7.47−7.32 (m, 3H), 6.45 (t, J = 1.1 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.70 (qd, J = 7.5, 1.1 Hz, 2H), 1.37−1.24 (m, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.0, 156.8, 155.9, 130.3, 129.0, 128.3, 128.1, 114.5, 107.4, 60.5, 21.3, 14.4, 12.0 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{16}NaO_3$, 267.0992; found, 267.0990; FTIR (neat): 2975, 1713, 1555, 1490, 1378, 1229 cm^{-1}. **4f′**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−7.98 (m, 2H), 7.64−7.56 (m, 1H), 7.53−7.44 (m, 2H), 4.78 (dd, J = 7.9, 6.3 Hz, 1H), 4.15 (qd, J = 7.1, 4.2 Hz, 2H), 3.53−3.26 (m, 2H), 2.58 (d, J = 1.0 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 193.7, 168.6, 136.2, 133.8, 128.9, 128.9, 98.3, 96.7, 61.9, 53.8, 49.1, 40.9, 14.1 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{16}I_2NaO_3$, 520.9082; found, 520.9078; FTIR (neat): 2979, 1736, 1686, 1596, 1447, 1369, 1234 cm^{-1}.

*Ethyl 2-Phenyl-5-propylfuran-3-carboxylate (**4g**).*[45] The cyclization of **3g** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/DCM (1:1) provided 54.2 mg of **4g** (41%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.93 (m, 2H), 7.46−7.34 (m, 3H), 6.46 (d, J = 0.9 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.65 (td, J = 7.4, 0.9 Hz, 2H), 1.73 (h, J = 7.4 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.0, 155.9, 155.4, 130.3, 129.0, 128.3, 128.1, 114.4, 108.2, 60.5, 29.9, 21.3, 14.4, 13.8 ppm.

*Methyl 2,5-Dimethylfuran-3-carboxylate (**4h**).*[54] The cyclization of **3h** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (20:1) provided 48 mg of **4h** (61%) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.19 (q, J = 1.2 Hz, 1H), 3.79 (s, 3H), 2.51 (s, 3H), 2.23 (d, J = 1.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (76 MHz, $CDCl_3$): δ 164.9, 157.9, 150.1, 113.8, 106.2, 51.3, 13.8, 13.3 ppm.

*Ethyl 2,5-Dimethylfuran-3-carboxylate (**4i**).*[10b] The cyclization of **3i** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (95:5) provided 68 mg of **4i** (70%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (d, J = 1.2 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.52 (s, 3H), 2.23 (d, J = 0.6 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.5, 157.7, 150.0, 114.1, 106.3, 60.0, 14.5, 13.8, 13.3 ppm.

*Benzyl 2,5-Dimethylfuran-3-carboxylate (**4j**).* The cyclization of **3j** was performed on a 1 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:1) provided 77 mg of **4j** (65%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.28 (m, 5H), 6.24 (q, J = 1.2 Hz, 1H), 5.26 (s, 2H), 2.53 (s, 3H), 2.23 (d, J = 1.3 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.2, 158.1, 150.1, 136.5, 128.7, 128.2, 128.1, 113.8, 106.4, 65.8, 13.9, 13.3 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{14}O_3Na$, 253.0836; found, 253.0836; FTIR (neat): 3033, 2951, 2921, 1710, 1587, 1498, 1397, 1360, 1278 cm^{-1}.

*Ethyl 5-Methyl-2-propylfuran-3-carboxylate (**4k**).*[55] The cyclization of **3k** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:1) provided 75 mg of **4k** (78%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24−6.17 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.24 (d, J = 1.1 Hz, 3H), 1.68 (h, J = 7.4 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.4, 161.7, 150.0, 113.9, 106.3, 60.0, 29.7, 21.7, 14.5, 13.9, 13.4 ppm.

*Ethyl 2-(tert-Butyl)-5-methylfuran-3-carboxylate (**4l**).*[44] The cyclization of **3l** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/Et_2O (20:1) provided 74 mg of **4l** (64%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (d, J = 1.1 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.23 (d, J = 1.1 Hz, 3H), 1.40 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.9, 164.2, 148.0, 112.7, 108.3, 60.1, 34.5, 28.4, 14.4, 13.2 ppm.

*Ethyl 5,5-Dimethyl-2-phenyl-4,5-dihydrofuran-3-carboxylate (**6a**).*[20] The cyclization of **5a** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 10:1) provided 91 mg of **6a** (74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78−7.70 (m, 2H), 7.43−7.32 (m, 3H), 4.12 (q, J = 7.1 Hz, 2H), 2.93 (s, 2H), 1.49 (s, 6H), 1.20 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.8, 164.1, 130.7, 130.2, 129.4, 127.7, 101.8, 85.6, 59.7, 44.4, 28.3, 14.4 ppm.

*Ethyl 2-(4-Bromophenyl)-5,5-dimethyl-4,5-dihydrofuran-3-carboxylate (**6b**).* The cyclization of **5b** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1) provided 113 mg of **6b** (70%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.91 (s, 2H), 1.48 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.6, 162.8, 131.0, 130.9, 129.5, 124.6, 102.3, 85.8, 59.8, 44.4, 28.3, 14.4 ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{17}{}^{79}BrO_3H$, 325.0434 and $C_{15}H_{17}{}^{81}BrO_3H$ 327.0414; found, 325.0435 and 327.0414; FTIR (neat): 2974, 2929, 2866, 1688, 1617, 1483, 1256 cm^{-1}.

*Ethyl 5,5-Dimethyl-2-(4-nitrophenyl)-4,5-dihydrofuran-3-carboxylate (**6c**).* The cyclization of **5c** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature, with 2 drops of DCE added to aid mixing. Purification by flash column chromatography and eluting with hexanes/EtOAc (50:1 to 10:1) provided 118 mg of **6c** (82%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22−8.17 (m, 2H), 7.97−7.92 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.95 (s, 2H), 1.49 (s, 6H), 1.21 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.1, 161.1, 148.4, 136.8, 130.5, 122.8, 104.6, 86.5, 60.1, 44.4, 28.2, 14.3 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{17}NO_5Na$, 314.0999; found, 314.0999; FTIR (neat): 3119, 2970, 2933, 2866, 1692, 1584, 1513, 1341, 1260 cm^{-1}.

*Ethyl 2-(4-Methoxyphenyl)-5,5-dimethyl-4,5-dihydrofuran-3-carboxylate (**6d**).* The cyclization of **5d** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/EtOAc (100:1 to 20:1) provided 75 mg of X (58%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.75 (m, 2H), 6.91−6.86 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 2.91 (s, 2H), 1.47 (s, 6H), 1.23 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.0, 164.0, 161.2, 131.1, 123.0, 113.0, 100.4, 85.1, 59.6, 55.4, 44.5, 28.3, 14.5 ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{20}O_4H$, 277.1435; found, 277.1436; FTIR (neat): 2974, 2936, 2843, 1692, 1606, 1509, 1245 cm^{-1}.

*Methyl 2,5,5-Trimethyl-4,5-dihydrofuran-3-carboxylate (**6e**).*[56] The cyclization of **5e** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Because **6e** is quite volatile, the yield of this reaction was determined to be 84% by ^{1}H NMR using 1,3,5-triisopropylbenzene as an internal standard. Purification by flash column chromatography and eluting with hexanes/EtOAc (50:1) provided **6e** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 3H), 2.67 (q, J = 1.6 Hz, 2H), 2.16 (t, J = 1.6 Hz, 3H), 1.37 (s, 6H)

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ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.2, 167.1, 100.9, 86.3, 50.9, 42.7, 28.4, 14.6 ppm.

*Ethyl 2,5,5-Trimethyl-4,5-dihydrofuran-3-carboxylate (**6f**).*[57] The cyclization of **5f** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Because **6f** is quite volatile, the yield of this reaction was determined to be 88% by ^1H NMR using 1,3,5-triisopropylbenzene as an internal standard. Purification by flash column chromatography and eluting with hexanes/EtOAc (20:1) provided **6f** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, J = 7.1 Hz, 2H), 2.67 (q, J = 1.6 Hz, 2H), 2.16 (t, J = 1.6 Hz, 3H), 1.37 (s, 6H), 1.26 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.8, 166.7, 101.2, 86.1, 59.4, 42.8, 28.4, 14.6, 14.6 ppm.

*Benzyl 2,5,5-Trimethyl-4,5-dihydrofuran-3-carboxylate (**6g**).*[20] The cyclization of **5g** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/Et_2O (50:1) provided 80 mg of **6g** (65%) as a light-yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.27 (m, 5H), 5.16 (s, 2H), 2.71 (q, J = 1.6 Hz, 2H), 2.18 (t, J = 1.6 Hz, 3H), 1.38 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.5, 166.4, 137.0, 128.6, 128.0, 128.0, 100.9, 86.4, 65.3, 42.7, 28.4, 14.7 ppm.

*Ethyl 5,5-Dimethyl-2-propyl-4,5-dihydrofuran-3-carboxylate (**6h**).* The cyclization of **5h** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1 to 50:1) provided 106 mg of **6h** (89%) as a light-yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.15 (q, J = 7.1 Hz, 2H), 2.68 (t, J = 1.1 Hz, 2H), 2.58 (ddt, J = 8.5, 7.4, 1.0 Hz, 2H), 1.64−1.51 (m, 3H), 1.37 (s, 6H), 1.27 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 170.4, 166.5, 100.8, 85.8, 59.3, 42.8, 29.9, 28.3, 20.4, 14.5, 13.8 ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{20}O_3Na$, 235.1305; found, 235.1306; FTIR (neat): 2970, 2933, 2873, 1695, 1636, 1371, 1263 cm^{-1}.

*Ethyl 2-(tert-Butyl)-5,5-dimethyl-4,5-dihydrofuran-3-carboxylate (**6i**).*[20] The cyclization of **5i** was performed on a 0.5 mmol scale with 15 mol % I_2 in 24 h at room temperature. Purification by flash column chromatography and eluting with hexanes/Et_2O (100:1 to 50:1) provided 49 mg of **6i** (42%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.12 (q, J = 7.1 Hz, 2H), 2.71 (s, 2H), 1.33 (s, 6H), 1.27 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 176.3, 166.0, 98.7, 84.2, 59.4, 44.7, 28.0, 27.6, 25.3, 14.6 ppm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00608.

Experimental details and spectroscopic data for all products, full Gaussian reference, Cartesian coordinates, and electronic and free energies (PDF)

Computational details (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Claude Y. Legault − *Department of Chemistry, Centre in Green Chemistry and Catalysis, Université de Sherbrooke, Québec J1K 2R1, Canada;* orcid.org/0000-0002-0730-0263; Email: claude.legault@usherbrooke.ca

Thanh Vinh Nguyen − *School of Chemistry, University of New South Wales, Sydney, New South Wales 2052, Australia;* orcid.org/0000-0002-0757-9970; Email: t.v.nguyen@unsw.edu.au

Authors

Domenic P. Pace − *School of Chemistry, University of New South Wales, Sydney, New South Wales 2052, Australia*

Raphaël Robidas − *Department of Chemistry, Centre in Green Chemistry and Catalysis, Université de Sherbrooke, Québec J1K 2R1, Canada*

Uyen P. N. Tran − *School of Chemistry, University of New South Wales, Sydney, New South Wales 2052, Australia; Van Hien University, Ho Chi Minh City, Vietnam*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00608

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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