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Authors

Dumas, Adrien
Garsi, Jean-Baptiste
Poissonnet, Guillaume
et al.

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Article

Ni-Catalyzed Reductive and Merged Photocatalytic Cross-Coupling Reactions toward sp^3/sp^2-Functionalized Isoquinolones: Creating Diversity at C-6 and C-7 to Address Bioactive Analogues

Adrien Dumas, Jean-Baptiste Garsi, Guillaume Poissonnet, and Stephen Hanessian*

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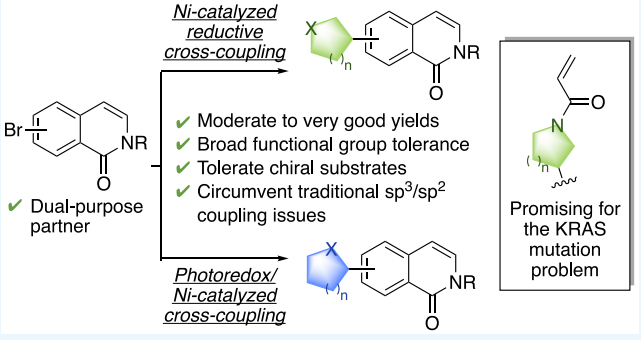
ABSTRACT: Naturally occurring isoquinolones have gained considerable attention over the years for their bioactive properties. While the late-stage introduction of various functionalities at certain positions, namely, C-3, C-4, and C-8, has been widely documented, the straightforward introduction of challenging sp^3 carbon-linked acyclic aminoalkyl or aza- and oxacyclic appendages at C-6 and C-7 remains largely underexplored. Interest in 6-substituted azacyclic analogues has recently garnered attention in connection with derivatives exhibiting anticancer activity. Reported here is the first application of the versatile and recently emerging field of Ni-catalyzed reductive cross-coupling reactions to the synthesis of 6- and 7- hetero(cyclo)alkyl-substituted isoquinolones. In a second and complementary approach, a new set of C-6- and C-7-substituted positional isomers of hetero(cyclo)alkyl appendages were obtained from the merging of photocatalytic and Ni-catalyzed coupling reactions. In both cases, 6- and 7-bromo isoquinolones served as dual-purpose reacting partners with readily available tosylates and carboxylic acids, respectively.



INTRODUCTION

Isoquinolones are among a small subgroup of heteroaromatic natural products isolated from plant sources.[1] They are frequently substituted with a hydroxy or methoxy group at C-6 (and C-7) as in doryphornine,[2] siamine,[3] coryaldine,[1] dorianine,[4] thalflavine,[5] and ruprechtstyril[6] (Figure 1).

The isoquinolone core motif can also be found in tricyclic alkaloids such as lycoricidine[7] and narciclasine.[8] The heteroaromatic bicyclic structure of isoquinolone encompassing a "cis-amide" group has long been recognized for its potential to mimic peptide sequences.[9] The utility of isoquinolones as core structures, upon which diverse functional groups can be introduced, has led to a plethora of compounds exhibiting anticancer,[10] antifungal,[11] antiallergic,[12] and antipsychotic[13] activities to mention a few (Figure 2).

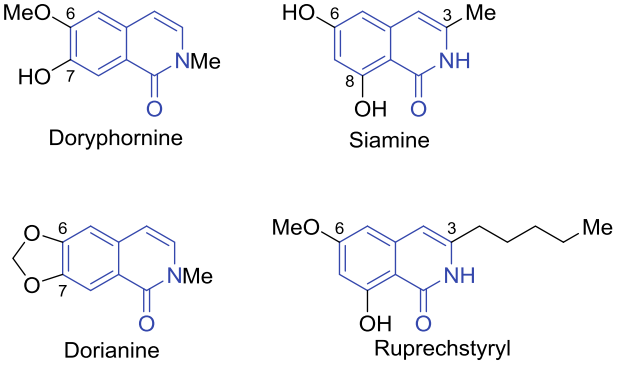


Figure 1. Selected isoquinolone natural products.

It is also of interest that a number of bioactive isoquinolones carry *N-substituents* in conjunction with carbon-bearing appendages at other positions.[14] The advent of transition-metal-catalyzed bond-forming reactions[15] has enabled the functionalization of diverse positions on aromatic and heteroaromatic rings. In the isoquinolone series, the C-3 position is amenable to substitution by means of a C−H activation process involving a directing group such as an *N*-pyridyl[16] or *N*-pyrimidyl[17] functionality. The inherent nucleophilic properties of isoquinolone, as well as the directing ability of the 1-oxo group, enable the introduction of substituents at C-4[18] and C-8,[16a,18a,b,19] respectively. A large variety of functionalities have thus been introduced on the isoquinolone skeleton including (hetero)aryls,[16c,e,17a,18a] alke-

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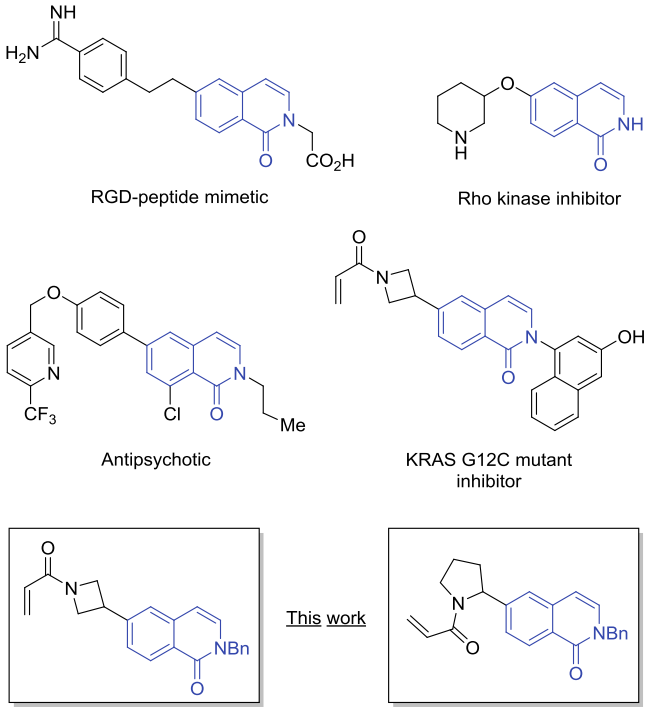

Figure 2. 6-Substituted bioactive isoquinolones and two prototypes from this work.

nes,[16h,17a,19] alkynes,[17b,18b] alkyls,[16b,d,g,k] dienes,[16j] and various heteroatoms.[16a,f,i,18c−h]

Direct introduction of substituents at C-6 and C-7 in isoquinolones is scarce and requires prefunctionalization. In this regard, 6-bromo isoquinolone is a pivotal substrate for the introduction of arene moieties at C-6, which can be readily achieved via metal-catalyzed arylation.[20] It is interesting to mention that the substitution of the 6-methoxy ether group in naturally occurring alkaloids such as doryphornine by ether-tethered azacyclic equivalents led to inhibitors of Rho kinase.[21] Increasing the sp^3 character of bioactive compounds often comprising stereogenic carbon atoms has proven beneficial for both their physical[22] and chemical properties.[22,23] There are, to the best of our knowledge, scant reports of isoquinolones that bear sp^3 carbon-linked acyclic aminoalkyl, or aza- and oxacyclic appendages at C-6 and C-7. The importance of the aforementioned modifications became evident with the recent report of 6-(3-azetidinyl-*N*-acryloyl) isoquinolones that show activity greater than 50% against KRAS G12C-mutant cancer cells after a 30 min incubation period (Figure 2).[24] This particular mutant has been labeled as an "undruggable" target in exploring elegant solutions to the KRAS mutation problem, as recently reported by the pioneering efforts by the Amgen group.[25] Being cognizant of the need to introduce related saturated heterocycles at positions 6 and 7 in the isoquinolone core by alternative methods, especially those containing usable functionality on resident stereogenic centers, we explored two complementary approaches toward this objective (Figure 3).

In the first of these, we were inspired by the scholarly contributions of Weix,[26] Gong,[27] and Molander[28] relying on well-precedented Ni-catalyzed reductive cross-coupling reactions involving alkyl (sp^3) and aryl or heteroaryl (sp^2) reacting partners.[29]

In the second approach, we capitalized on the recent innovative methods of merged photocatalytic and Ni-catalyzed

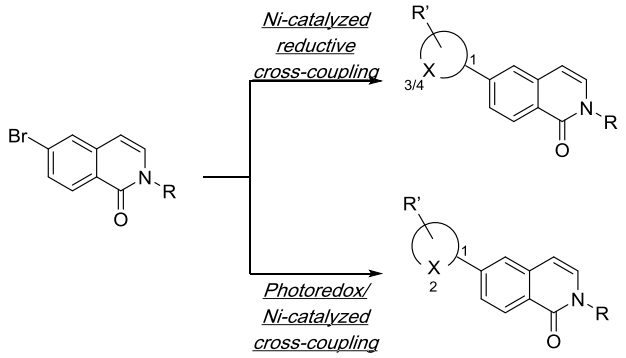

Figure 3. 6-Bromo isoquinolone: a dual-purpose cross-coupling partner.

coupling reactions pioneered by MacMillan[30,31] to forge the same reaction between heteroaryl and a series of aza- and oxacyclic α-carboxylic acids toward C-6 and C-7 sp^3/sp^2-substituted isoquinolones for the first time.

RESULTS AND DISCUSSION

We began our investigations with the Ni-catalyzed reductive cross-coupling reaction of *N*-benzyl 6-bromo isoquinolone **1a** with *N*-Boc-4-tosyloxy-piperidine (**2a**) as a test substrate following similar conditions established by Molander and co-workers[28b] (Scheme 1). Thus, using 3 equiv of the tosylate, $NiBr_2$·glyme (5 mol %), 4,4′-di-*tert*-butyl 2,2′-dipyridyl (4,4′-dtbp) (5 mol %), Mn^0 as the reductant (2 equiv), KI (1 equiv), 4-ethyl pyridine (1 equiv), and *N*,*N*-dimethylacetamide (DMA) as solvent at 80 °C led to the desired cross-coupling product **3** in a 90% yield and only trace amounts of biaryl byproduct **4**. Following the same general protocol, we engaged the tosyloxy derivatives of a variety of azacyclic and oxacyclic compounds in the same cross-coupling reaction to furnish the corresponding C-6-substituted *N*-Bn-isoquinolones. The resulting racemic compounds **5**−**12** consisted of equimolar mixtures of enantiomers. In general, and with few exceptions, yields were good to excellent with varying amounts of the biaryl byproduct **4** being formed depending on the substrate, especially when the yields were low. For example, biaryl formation varying from 21 to 40% was observed in the case of **5**, **9a**, **18**, **19**, and **20**, as well as some debrominated starting material. Exceptionally, *N*-Boc 3-tosyloxy azetidine required only 1 equiv to give compound **9a** in a 50% yield, while the expected product **10** from 3-tosyloxy oxetane remained unreactive. 4-Tosyloxy tetrahydropyran and 3-tosyloxy tetrahydrofuran were good substrates affording the corresponding products **11** and **12**, respectively, in good yields. The occurrence of *N*-methyl isoquinolones in nature (Figure 1) led us to test the cross-coupling reaction with *N*-methyl 6-bromo isoquinolone **1b**. *N*-Me heterocycles are also widely recognized as an important class of biologically relevant compounds.[32] The expected products **6** and **8** were formed in moderate to excellent yield, respectively (Scheme 1). The position of the tosylate ester with regard to the *N*-Boc group, particularly in the case of the piperidines, appeared to affect the yield (compare **3** and **5**). The substantially lower yield in the cross-coupling of **1a** with racemic *N*-Boc 3-tosyloxy piperidine **2b** compared to that of the symmetrical 4-tosyloxy counterpart **2a** could be due to steric, conformational, or coordination effects leading to an inefficient participation in the catalytic cycle (Scheme 2, Table 1, entries 1 and 2). The same

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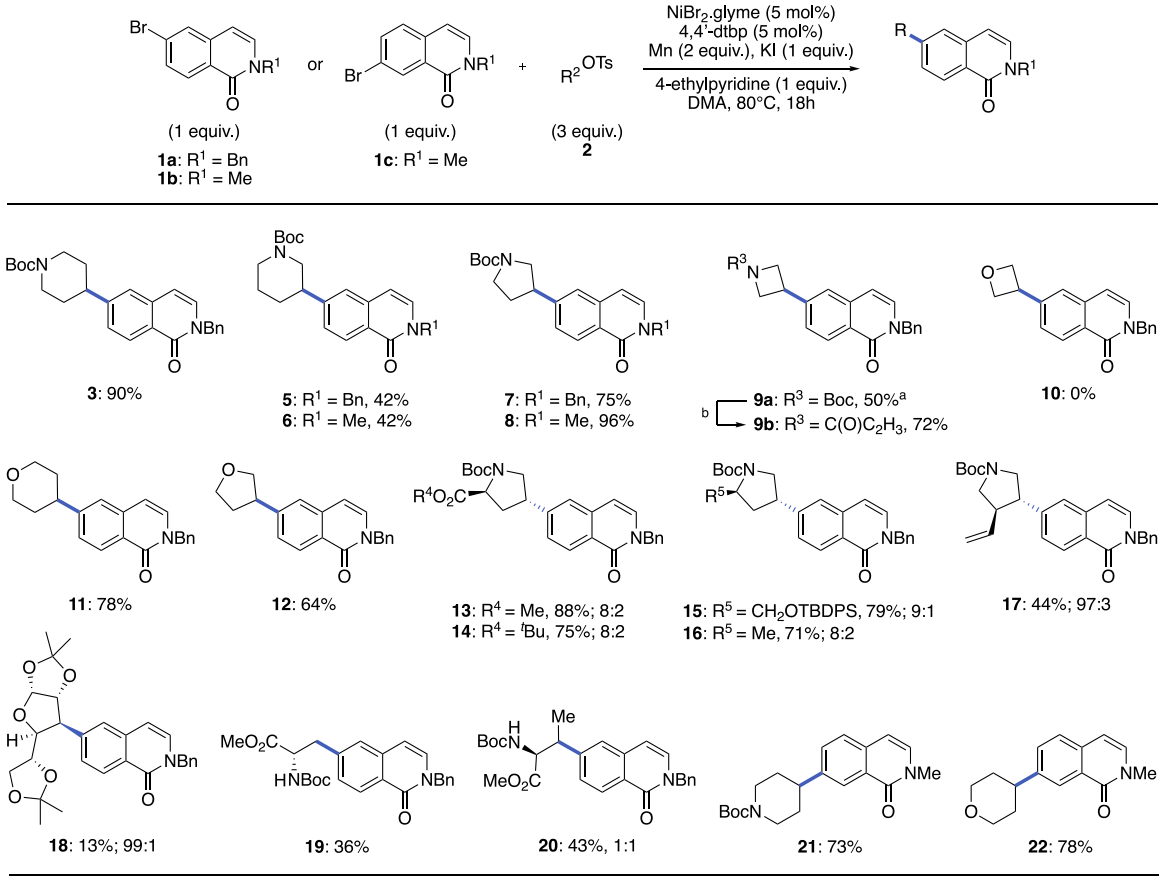
Scheme 1. Ni-Catalyzed Reductive Cross-Coupling Reactions Leading to 6- and 7-Substituted Isoquinolones



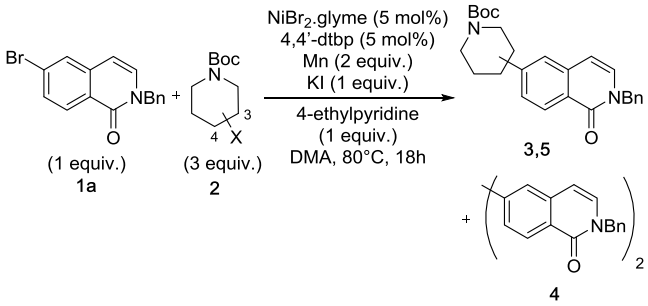
[a]1 equiv instead of 3 equiv. [b](1) HCl/dioxane, rt, 2 h; (2) acryloyl chloride, Et3N, CH2Cl2, rt, 18 h.

observation was made by Molander in the reaction of 6-bromoindole with *N*-Boc 3- and 4-tosyloxy piperidines.[28b]

With the successful application of the original Molander conditions[28b] with achiral and racemic tosyloxy aza- and oxacycles, we extended our study to chiral nonracemic azacyclic tosylates derived from the readily available *N*-Boc 4(*R*)-tosyloxy-L-proline methyl ester as well as the corresponding 5-*O*-*tert*-butyldiphenylsilyl-L-prolinol and related pyrrolidine derivatives. We were delighted that very good yields were obtained and that the products **13**−**16** were highly enriched in the *trans*-diastereomers as revealed by NMR analysis. Compound **13** could be transformed to the same $CH_2OTBDPS$ congener **15**, thereby establishing their interrelationship as well as their similar reactivity and diastereoselectivity. In spite of the modest yield of the vinyl analogue **17**, the trend for conservation of the original *trans*-relationship was maintained. The same sterically controlled reaction was observed for the sugar derivative **18** albeit obtained in poor yield. The tosylates of *N*-Boc L-serine methyl ester and *N*-Boc L-threonine methyl ester are also suitable substrates for cross-coupling affording compounds **19** and **20** in modest yields. Extending the cross-coupling reactions to *N*-methyl 7-bromo isoquinolinone **1c** was equally successful as evidenced by the formation of the *N*-Boc 4-piperidinyl and 4-tetrahydropyranyl products **21** and **22** in good yields.

Although we adopted the experimental conditions reported by the scholarly studies of Molander,[28b] we made several observations that appear to be germane to an *N*-alkyl 6-bromo

Scheme 2. Table 1. Evaluation of Experimental Conditions



entry	(Pseudo)halide X	Variation from the standard conditions	Yield 3,5 (%)[a]	Yield 4 (%)[a]
1	2a (X = 4-OTs)	-	90	<5
2	2b (X = 3-OTs)	-	42	21
3	2b (X = 3-OTs)	5 equiv. 2b vs. 3 equiv.	41	19
4	2b (X = 3-OTs)	1 equiv. 2b vs. 3 equiv.	21	37
5	2b (X = 3-OTs)	0.2 equiv. [Ni] & 4,4'-dtbp	42	35
6	2c (X = 3-SO_2-2py)	1 equiv. 2c vs. 3 equiv.	19	30
7	2d (X = 3-SO_2-3py)	1 equiv. 2d vs. 3 equiv.	12	31
8	2a (X = 4-OTs)	without KI	<5	0
9	2a (X = 4-OTs)	nBu_4NI vs. KI	53	<5
10	2e (X = 4-I)	-	71	0
11	none	-	0	8[b]

[a]Isolated yield. [b]Also contained a mixture of dehalogenated-**1a**:**1a**:6-iodo isoquinolone in a 4:62:34 ratio.

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isoquinolone as a reactive partner, possibly due to its particular electronic heteroaromatic character.

Using the test substrates *N*-Boc 4- and 3-tosyloxy piperidines **2a** and **2b**, we conducted experiments to assess the importance of the stoichiometry of the substrates and the reagents (Scheme 2, Table 1, entries 1−4). Whereas 1 equiv of the tosyloxy compounds **2** was required in the Molander cross-coupling reactions within the *N*-Boc 6-bromoindole series, which resulted in modest to good yields of coupled products,[28b] 3 equiv of tosyloxy compounds **2a** was needed in our case to achieve preparatively significant to modest yields. To improve the yield of the 3-substituted *N*-Boc-piperidine product **5**, we increased the concentration of the tosyloxy precursor **2b** to 5 equiv without affecting the yield (Scheme 2, Table 1, entry 3). However, increasing the catalyst and ligand concentration to 20 mol % (Scheme 2, Table 1, entry 5) resulted in 35% of the biaryl dimer **4**, consistent with Weix's observations.[33] Only in the case of the azetidine analogue **9a** did we succeed in obtaining 50% yield with 1 equiv of the tosyloxy substrate (Scheme 1) accompanied by dimer (23%). Curiously, the oxetane derivative **10** was not formed (Scheme 1). It is of interest that under the same conditions, Molander reported that 3-tosyloxy *N*-Boc-azetidine and 3-tosyloxy oxetane failed to react with *N*-Boc 6-bromoindole.[28b] However, in the latter case, reaction occurred in the presence of $MgCl_2$ as an additive and Mn as the reductant, under otherwise similar conditions, to afford the expected 6-oxetanyl *N*-Boc indole.[28a] Dimerization of the isoquinolone to **4** was the main process when yields of cross-coupled products were low or modest. Using the same reaction conditions but in the absence of the tosylate ester **2** resulted in the formation of 8% of dimer **4** and an inseparable mixture of dehalogenated-**1a**, **1a** and *N*-benzyl 6-iodo isoquinolone in a 4:62:34 ratio (Scheme 2, Table 1, entry 11). This result was surprising, and it appears that the presence of the alkyl tosylate among the other components in the reaction mixture plays a role in determining the distribution of products. In an effort to explore a possible coordination with the catalyst,[34] we tried the cross-coupling reaction of **1a** with the (2-pyridyl) and (3-pyridyl) sulfonate esters **2c** and **2d** of *N*-Boc 3-hydroxypiperidine. Unfortunately, the amount of biaryl **4** was increased (∼30%) at the expense of the desired cross-coupling product **5** (19 and 12%, respectively) (Scheme 2, Table 1, entries 6 and 7).

The mechanism of direct Ni-catalyzed sp^3/sp^2-reductive cross-coupling reactions between aryl halides and nonactivated alkyl halides not involving preformed organometallic reagents has been the object of elegant studies.[29b,e,33,35] The original Weix protocol for Ni-catalyzed reductive couplings of aryl halides and unactivated alkyl halides[26a] has undergone some subtle changes[33] with regard to the Ni-coordinating ligand, the reducing metal, the base, and the solvent. In the Molander protocol that we adopted in our study of *N*-Boc 4-tosyloxy piperidine, the inclusion of KI and 4-ethyl pyridine was deemed to be important additives to ensure better efficiency.[28b] The role of KI as an additive during the catalytic cycle of these reductive Ni-catalyzed cross-coupling reactions has been discussed in several reports.[26b,28b,36] Among the different possibilities,[37] it has been suggested that the KI could also facilitate ligand exchange.[38] An in situ displacement of the tosyloxy group to generate the corresponding iodide as the reactive partner has been discussed by Molander,[28b] Weix,[26b,36] and Gong.[39] However, in the Molander study with *N*-Boc 6-bromoindole, *N*-Boc 4-iodo piperidine was unreactive with and without KI. In our case, the cross-coupling of *N*-Boc 6-bromo isoquinolone **1a** with *N*-Boc 4-iodo piperidine **2e** under the same conditions afforded a 71% yield of coupled product **3** with and without KI (Scheme 2, Table 1, entry 10). A control experiment revealed that potassium iodide efficiently converted *N*-Boc 4-tosyloxy piperidine into the corresponding iodide in DMA at 80 °C (see the Supporting Information for details). It has been suggested that the use of Bu_4NI could increase the ionic strength of the medium and enhance reactivity.[40] However, in our case with *N*-Boc 4-tosyloxy piperidine **2a**, replacing KI with Bu_4NI significantly reduced the yield of the product (53%) (Scheme 2, Table 1, entry 9). Omitting the salt resulted in the recovery of both reactants in almost quantitative yield (Scheme 2, Table 1, entry 8).

Added to this intricate protocol, in which the Molander conditions were simulated,[28b] is the presumed beneficial role of a weakly basic entity such as pyridine as an additive. We were intrigued by the role of 4-ethyl pyridine as an additive in the reaction conditions used by Molander. Literature reports suggest that a base may contribute to the efficiency of the reaction,[26a] although its actual role has not been definitively established. We were surprised that the cross-coupling reaction could be successfully achieved in the *absence* of 4-ethyl pyridine to give compound **3** in an 87% yield. The same trend was observed with **7** (70%) and **13** (81%) with minor variations compared to the presence of the base. With these results, the roles of KI and 4-ethyl pyridine as they relate to discrete intermediates in the catalytic cycle of the reductive cross-coupling of *N*-benzyl 6-bromo isoquinolone and nonactivated alkyl electrophiles present a substrate-dependent conundrum that merits further study in the future.

Adopting the mechanism postulated by Weix,[33] the oxidative addition of the *N*-benzyl 6-bromo isoquinolone **1a** to the Ni^0 catalyst generates $ArNi^{II}Br$ and an alkyl radical leads to an $ArNi^{III}RBr$ intermediate where cross-coupling takes place to give Ar-R. A second radical is generated from the alkyl electrophile via a Ni^I specie, which re-enters the catalytic cycle in what amounts to a radical chain process. A double oxidative mechanism has also been proposed by Gong and studied by density functional theory (DFT) analysis.[35a,c] Although the formation of alkyl radicals has been invoked in these Ni-catalyzed reductive cross-coupling reactions, no dimer formation was observed in spite of using 3 equiv of tosylate **2a** or the iodide (**2e**, OTs = I), which may reflect on the relative reactivity of the substrate-bound Ni-coordinated intermediates and the rate at which radicals are formed and engaged in the catalytic cycle.[41] Dimer formation from 6-bromo isoquinolone **1a** in some reactions but not others under essentially the same conditions with different alkyl tosylates remains to be further investigated. The successful cross-coupling of *N*-Boc 4(*R*)-tosyloxy-L-proline methyl ester and its analogues to provide the *trans*-azacyclic adducts **13**−**16** as the major products in excellent yield reflects the importance of steric effects and supports the formation of free radicals. To shed more light on the stereochemical course of the reaction, we show that cross-coupling of *N*-Boc 3(*R*)-tosyloxy pyrrolidine ((***R***)-**23**) and 3(*S*)-tosyloxy pyrrolidine ((***S***)-**23**) under the standard conditions led to the racemic adduct **7** in 79 and 75% yields, respectively (Scheme 3). Stereochemical erosion during related Ni-catalyzed reactions involving substrates has been ascribed to the intermediate formation of radicals.

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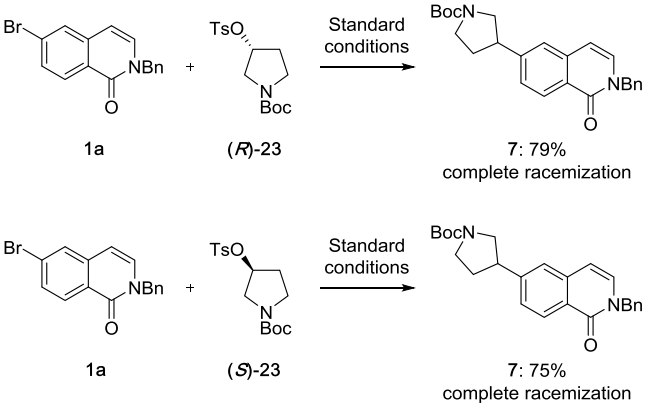
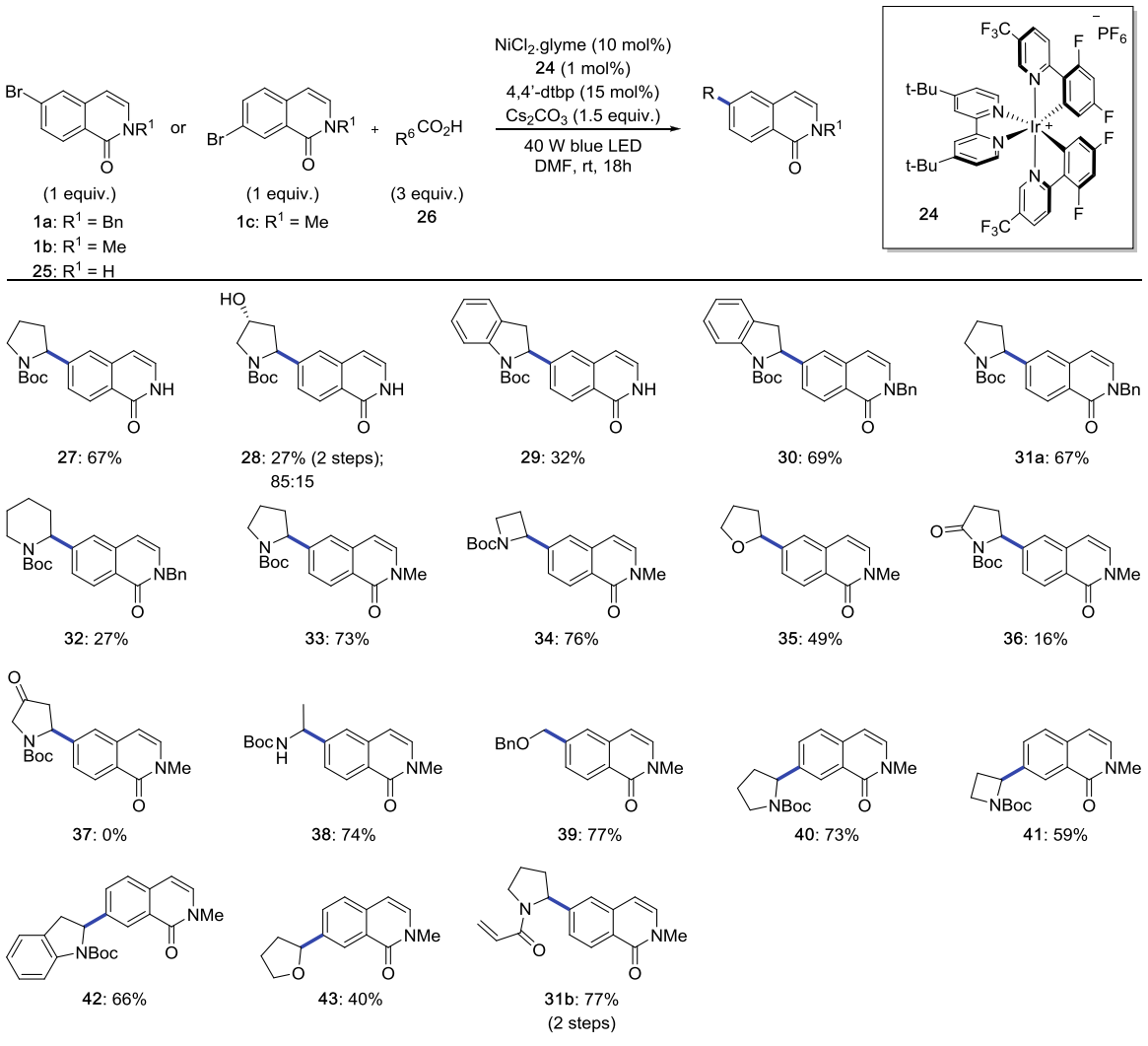
Scheme 3. Stereochemical Course of the Ni-Reductive Cross-Coupling Reaction



The intermediacy of alkyl radicals in Ni-catalyzed cross-coupling reactions of alkyl halides has been discussed in different contexts.[42] It has been suggested that because of the high-lying antibonding orbital of the C−O bond, alkyl tosylates fail to form alkyl radicals in single electron-transfer processes;[43] hence, they are less prone to undergo oxidative addition via a radical pathway. However, there are examples of Ni-catalyzed cross-coupling reactions of alkyl sulfonates under reductive conditions, especially in the presence of activating agents.[27b,28b,36,41,43a,e,44] From a reactivity standpoint, radicals generated from alkyl iodides should be the preferred partners in metal-catalyzed reductive cross-couplings.[43d] With our limited knowledge of the nature of discrete Ni-coordinated intermediates and their reactivity during the catalytic cycle in cross-coupling reactions of **1** with the alkyl tosylates used in this study, we should question if the efficiency of the reactions depends not only on whether iodides are the actual intermediates in certain cases but also on the nature of the substrate. For example, compounds **3**, **8**, **13**, and **15** were produced in excellent yields from the corresponding azacyclic tosylates, but others were less performing (Scheme 1). In a future study, it would be informative to compare the reactivities of the less efficient tosylates versus their iodide counterparts.[45] Besides the use of radical clocks to study the intermediacy of radicals,[46] it is known that radicals can be inhibited with single electron-transfer reagents.[47] We were therefore intrigued that the cross-coupling reaction of **1a** and **2a** took place in the presence of BHT (2,6-di-*tert*-butyl-4-methylphenol) (0.5 equiv) as well as with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) leading to compound **3** in yields of

Scheme 4. Dual Photoredox/Ni-Catalyzed Cross-Coupling Reactions of 6- and 7-Bromo Isoquinolones



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66 and 35%, respectively, with no significant dimer formation. The inefficient trapping of a radical may be due to the proportion of Ni-bound and unbound radicals. Partial poisoning of the catalyst has been invoked in a different context.[48] No reaction took place in the presence of 1-chloro-2,4-dinitrobenzene.[47] The Reisman group developed asymmetric reductive cross-coupling reactions between vinyl and benzyl halides for which neither the addition of BHT or the use of a radical clock substrate succeeded in highlighting the presence of radicals.[49a] However, Biswas and Weix[33] observed rearrangement in a radical clock substrate, but the radical could not be trapped by BHT.

In the context of introducing functionally versatile substituents at the 6- and 7-positions of *N*-Boc isoquinolone, we wished to change the site of attachment to the α-carbon atom of azacyclic-, oxacyclic-, and selected acyclic-related entities. The availability of the corresponding carboxylic acids of such compounds offered an excellent opportunity to explore the innovative merged photoredox/Ni-catalyzed decarboxylative cross-coupling strategy recently developed by MacMillan using an iridium catalyst.[40,50] We took notice that in spite of numerous applications, this method was yet to be applied to isoquinolones. We adopted the same protocol as directed by MacMillan,[50b] utilizing the Ir catalyst **24** and 3 equiv of the carboxylic acid **26**. Thus, the decarboxylative coupling[51] reaction of unprotected 6-bromo isoquinolone **25** with *N*-Boc-proline led to racemic **27** in a 67% yield (Scheme 4).

However, the efficiency of the coupling appeared to be substrate-dependent as a significant drop in yield was observed when the reaction was performed with *N*-Boc-4(*R*)-*tert*-butyldiphenylsilyloxy L-proline producing **28** (27%) over two steps as an 85:15 trans/cis mixture of isomers. This was in line with the preferential formation of *trans*-isomers from related azacyclic tosylates in the Ni-catalyzed reductive cross-coupling reactions (Scheme 1).[50c] The reaction with *N*-Boc indoline-2-carboxylic acid afforded **29** (32%) and debrominated isoquinolone (25%). Performing the same reaction with *N*-benzyl 6-bromo isoquinolone **1a** resulted in improved yields. Thus, the coupling of **1a** with *N*-Boc indoline-2-carboxylic acid led to a 69% yield of **30** without any observable debromination. Coupling with *N*-Boc L-proline and (*S*)-*N*-Boc piperidine-2-carboxylic acid with **1a** delivered **31a** (67%) and **32** (27%), respectively, as racemates. The low yield of **32** was due to partial conversion under standard reaction time (33% conversion, 82% yield based on the recovered material). Extended reaction times failed to improve the yield as substantial degradation was observed over a period of 72 h. As in the case of the Ni-catalyzed cross-coupling reactions (Scheme 1), *N*-methyl 6-bromo isoquinolone performed better than the corresponding *N*-benzyl counterpart, leading to **33** in a 73% yield. The photoredox cross-coupling with azacyclic and oxacyclic carboxylic acids was successfully extended to produce the 6-substituted *N*-methyl isoquinolones harboring a 2-azetidinyl (**34**, 76%) and a 2-tetrahydrofuranyl appendage (**35**, 49%), respectively, as racemates (Scheme 4). A poor yield resulted from the cross-coupling reaction with *N*-Boc (*R*)-pyroglutamic acid (**36**, 16%). No cross-coupling took place with 3-oxo *N*-Boc (*R*)-pyroglutamic acid (compound **37**, Scheme 4).

The cross-coupling reaction could be applied to acyclic carboxylic acids represented by *N*-Boc-alanine and 2-(benzyloxy)-acetic acid giving the corresponding 6-substituted products **38** (74%) and **39** (77%), respectively. In analogy with the Ni-catalyzed reductive cross-coupling reactions, we sought to extend the photoredox cross-coupling to the 7-position of the isoquinolone ring. Cross-coupled racemic products **40** and **41** were obtained in 73 and 59% yields from *N*-Boc L-proline and *N*-Boc-azetidine carboxylic acid, respectively. In the latter case, 91% conversion and 4% debrominated-**1c** were observed. Interestingly, even though the yield of **42** (66%) was not decreased compared to the analogous product **30** at the 6-position, 25% of debrominated-**1c** was observed. The 2-tetrahydrofuranyl analogue **43** was prepared in modest yield. Finally, racemic *N*-methyl 6-(2-*N*-acryloyl pyrrolidinyl) isoquinolone **31b** (77% for two steps) was prepared for prospective testing as an anticancer agent.[24]

The mechanism of the merged photoredox and Ni-catalyzed decarboxylative cross-coupling reactions has been elegantly investigated by MacMillan,[50] and the intermediacy of radicals as single electron entities has been demonstrated.[50b] With few exceptions in the current 6-bromo isoquinolone series, yields were consistently good, which reflects on the relative stability of the radicals next to the electron-withdrawing *N*-Boc group. In this regard, the fate of the radicals may be more predictable compared to that of the Ni-catalyzed reductive cross-coupling reactions in the same series (Scheme 1). It is also clear that the electron-withdrawing groups such as a carbonyl are detrimental to the cross-coupling (Scheme 4, **36**, **37**). In the absence of steric effects from resident groups on stereogenic carbon atoms in the enantiopure carboxylic acids, the loss of chirality of amino acids and related heterocyclic compounds would be expected from the generated α-carbamoyl-stabilized free radicals. In this regard, Fu and MacMillan have reported on innovative ways to maintain high stereogenicity in the merged photoredox Ni-catalyzed cross-couplings with α-amino acids using chiral ligands.[40] In contrast, in spite of the wide applicability of the method, some exceptions were notable. For example, *N*-Boc L-proline and *N*-Boc L-valine were not suitable partners when cross-coupled to aryl and heteroaryl halides, possibly due to steric effects as reported by Fu and MacMillan.[40]

CONCLUSIONS

In conclusion, we have successfully achieved the Ni-catalyzed cross-coupling reaction of *N*-Boc 6-bromo isoquinolone with 3- and 4-tosyloxy *N*-Boc piperidines, 3-tosyloxy *N*-Boc pyrrolidines, 4-tosyloxy tetrahydropyran, and 3-tosyloxy tetrahydrofuran toward the synthesis of novel 6-substituted isoquinolones containing appended azacyclic and oxacyclic motifs. The reaction could be extended to *N*-methyl 7-bromo isoquinolone. Using chiral nonracemic tosyloxy esters derived from a prototypical sugar derivative, and *N*-Boc amino acid methyl ester and related derivatives of L-proline, the cross-coupling reaction with *N*-benzyl 6-bromo isoquinolone gave access to the corresponding diastereomerically highly enriched *N*-Boc 6-substituted isoquinolones for the first time in this series (Scheme 1). Reactions with tosylates derived from acyclic amino acid derivatives such as L-serine and L-threonine were equally possible albeit in lower yields. Having adopted the original methodology reported by Molander and inspired by the mechanistic insights of Weix,[29b,33] Gong,[35a,c] and Diao,[35b] our own Ni-catalyzed cross-coupling study of 6- and 7-bromo isoquinolones with unactivated primary and secondary tosylate esters allowed us to make pertinent observations with regard to the role of additives such as KI and 4-ethyl pyridine. The successful adaptation of the MacMillan-merged photoredox

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and Ni-catalyzed cross-coupling to a number of saturated heterocyclic and acyclic α carboxylic acids complements the reductive cross-coupling reactions and highlights the use of 6-bromo *N*-alkyl isoquinolones as dual-purpose partners. The timely discovery that acrylamide derivatives of 6-azacyclic *N*-aryl isoquinolones possess anticancer activity[24] augurs well to extend the scope of our work toward related positional isomers as covalent inhibitors in biological targets.[52]

Although the preparative aspects of the Ni-catalyzed reductive and merged photoredox cross-coupling reactions were achieved using methods essentially developed by the Molander and MacMillan groups, respectively, certain enigmatic observations made during the course of this study remain germane to the use of *N*-alkyl 6- and 7-bromo isoquinolones as the aryl partner and reflect on the complexity of generalized mechanistic interpretations.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all of the reactions were carried out using standard Schlenk techniques. Glassware was oven- (135 °C) or flame-dried prior to use. Anhydrous dichloromethane and tetrahydrofuran (THF) were obtained using solvent purification system. Dimethylacetamide and dimethylformamide were purchased at Sigma-Aldrich with a Sure/Seal packaging. Potassium iodide was flame-dried in a flask under vacuum prior to use. All other solvents and reagents were used as received. For photocatalytic reactions, a 40 W blue LED Kessil lamp was used. Reactions were monitored by thin-layer chromatography carried out on a 0.25 mm silica plate (SIL 60, G-25, UV254) and were visualized using a UV lamp (254 nm). NMR spectra were recorded on Bruker AV-300, ARX-400, AV-400, or AV-500 spectrometers with complete proton decoupling for nucleus other than ^{1}H. ^{1}H and ^{13}C chemical shifts are reported in parts per million with the solvent resonance as the internal standard ($CDCl_3$, ^{1}H: δ 7.26 ppm, ^{13}C: δ 77.16 ppm). Coupling constants are reported in Hertz (Hz). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sept = septuplet, dd = double doublet, dt = double triplet, ddd = double double doublet, dtt = double triple triplet, m = multiplet, br = broad. Spectra were analyzed and processed using MestReNova. High-resolution mass spectrometry (HRMS) analysis was performed at the Centre Régional de Spectrométrie de Masse de l'Université de Montréal. *Important information*: Tosylates might not always easily solidify after purification. Coevaporation with pentane and/or adding hexane and allowing the solution to sonicate in an ultrasound bath generally helped for solidification.

We observed a better reproducibility of the Ni-catalyzed coupling reactions when solid tosylates were used.

*tert-Butyl 4-(Tosyloxy)piperidine-1-carboxylate (**2a**).* *N*-Boc-4-hydroxypiperidine (2 g, 9.94 mmol, 1 equiv) in dichloromethane (25 mL) was treated by tosyl chloride (2.8 g, 14.9 mmol, 1.5 equiv) and 4-dimethylaminopyridine (DMAP, 364 mg, 2.98 mmol, 0.3 equiv) at rt. Then, triethylamine (2.8 mL, 19.9 mmol, 2 equiv) was added and the resulting mixture was stirred overnight at rt. Excess tosyl chloride was readily decomposed upon the addition of *N*,*N*-dimethylethylenediamine and stirring for 10 min at room temperature. Water was added to the mixture, and the product was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification on SiO_2 using hexane/EtOAc = 90/10−80/20 led to the isolation of **2a** as a white solid (3.03 g, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.66 (tt, J = 7.4, 3.8 Hz, 1H), 3.64−3.51 (m, 2H), 3.24 (ddd, J = 13.6, 7.5, 4.1 Hz, 2H), 2.44 (s, 3H), 1.82−1.59 (m, 4H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 144.9, 134.4, 130.0, 127.7, 80.0, 78.2, 40.4, 31.4, 28.5, 21.8. HRMS (ESI) calcd for $C_{17}H_{25}NO_5S$ (M + Na)+: m/z 378.13456, found: 378.13556 (−2.64 ppm).

*tert-Butyl 3-(Tosyloxy)piperidine-1-carboxylate (**2b**).* Tosyl chloride (1.4 g, 7.46 mmol, 1.5 equiv) in dichloromethane (8 mL) was treated by trimethylamine hydrochloride (47 mg, 0.50 mmol, 0.1 equiv) and triethylamine (1.4 mL, 9.94 mmol, 2 equiv) at 0 °C. Then, *N*-Boc-3-hydroxypiperidine (1 g, 4.97 mmol, 1 equiv) in dichloromethane (2 mL) was added at 0 °C. The resulting mixture was stirred overnight. Excess tosyl chloride was readily decomposed upon the addition of *N*,*N*-dimethylethylenediamine and stirring for 10 min at room temperature. Water was added to the mixture, and the product was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification on SiO_2 using hexane/EtOAc = 80/20 led to the isolation of **2b** as a white solid (1.64 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.77 (m, 2H), 7.37−7.30 (m, 2H), 4.45 (br s, 1H), 3.55 (dd, J = 13.6, 3.1 Hz, 1H), 3.46−3.18 (m, 3H), 2.44 (s, 3H), 1.92−1.66 (m, 3H), 1.52−1.40 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 144.8, 134.3, 130.0, 127.8, 80.1, 75.9, 48.5, 43.5, 30.4, 28.4, 22.0, 21.8. HRMS (ESI) calcd for $C_{17}H_{25}NO_5S$ (M + Na)+: m/z 378.13456, found: 378.1347 (−0.35 ppm).

*tert-Butyl 3-(Pyridin-2-ylsulfonyl)piperidine-1-carboxylate (**2c**).* 2-Pyridylsulfonyl chloride (612 mg, 3.45 mmol, 1.4 equiv) in dichloromethane (5 mL) was treated by trimethylamine hydrochloride (233 mg, 2.46 mmol, 1 equiv) and triethylamine (0.69 mL, 4.96 mmol, 2 equiv) at 0 °C. Then, *N*-Boc-3-hydroxypiperidine (495 mg, 2.46 mmol, 1 equiv) in dichloromethane (2 mL) was added. The resulting mixture was stirred overnight at 0 °C. Water was added to the mixture, and the product was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification on SiO_2 using hexane/EtOAc = 60/40 led to the isolation of **2c** as a colorless thick oil (560 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (ddd, J = 4.7, 1.8, 0.9 Hz, 1H), 8.03 (dt, J = 7.9, 1.1 Hz, 1H), 7.94 (td, J = 7.7, 1.7 Hz, 1H), 7.56 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 4.98−4.88 (m, 1H), 3.68−3.18 (m, 4H), 2.10−1.69 (m, 3H), 1.53−1.42 (m, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.7, 150.4, 138.4, 127.7, 126.6, 123.0, 80.1, 78.6, 48.7, 43.1, 30.5, 28.4, 21.8. HRMS (ESI) calcd for $C_{15}H_{22}N_2O_5S$ (M + Na)+: m/z 365.11416, found: 365.11457 (−1.11 ppm).

*tert-Butyl 3-(Pyridin-3-ylsulfonyl)piperidine-1-carboxylate (**2d**).* 3-Pyridylsulfonyl chloride (505 mg, 2.84 mmol, 1.4 equiv) in dichloromethane (5 mL) was treated by trimethylamine hydrochloride (194 mg, 2.03 mmol, 1 equiv) and triethylamine (0.57 mL, 4.06 mmol, 2 equiv) at 0 °C. Then, *N*-Boc-3-hydroxypiperidine (409 mg, 2.03 mmol, 1 equiv) in dichloromethane (1 mL) was added. The resulting mixture was stirred overnight at 0 °C. Water was added to the mixture, and the product was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification on SiO_2 using hexane/EtOAc = 60/40 led to the isolation of **2d** as a white solid (627 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (dd, J = 2.4, 0.8 Hz, 1H),

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8.86 (dd, J = 4.9, 1.7 Hz, 1H), 8.20 (dt, J = 8.2, 2.0 Hz, 1H), 7.50 (ddd, J = 8.1, 4.9, 0.9 Hz, 1H), 4.61 (br s, 1H), 3.59−3.46 (m, 2H), 3.42−3.22 (m, 2H), 1.93−1.68 (m, 3H), 1.52−1.44 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ = 154.6, 154.4, 148.5, 135.4, 134.2 124.0, 80.3, 76.9, 48.6, 47.2, 43.9, 43.0, 30.3, 28.4, 21.7. HRMS (ESI) calcd for $C_{15}H_{22}N_2O_5S$ (M + Na)+: m/z 365.11416, found: 365.11454 (−1.02 ppm).

*tert-Butyl (2S,4R)-2-(((tert-Butyldiphenylsilyl)oxy)methyl)-4-(tosyloxy)pyrrolidine-1-carboxylate (**S1**).* Tosyl chloride (240 mg, 1.26 mmol, 1.5 equiv) in dichloromethane (4 mL) was treated by trimethylamine hydrochloride (8 mg, 0.084 mmol, 0.1 equiv) and triethylamine (0.23 mL, 1.68 mmol, 2 equiv) at 0 °C. Then, *N*-Boc-(2*S*,4*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxypyrrolidine (384 mg, 0.84 mmol, 1 equiv) in dichloromethane (1 mL) was added at 0 °C. The resulting mixture was stirred for 3 h. Excess tosyl chloride was readily decomposed upon the addition of *N*,*N*-dimethylethylenediamine and stirring for 10 min at room temperature. Water was added to the mixture, and the product was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification on SiO_2 using hexane/EtOAc = 90/10 led to the isolation of **S1** as a white solid (340 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.76 (d, J = 7.0 Hz, 2H), 7.57 (dd, J = 16.3, 10.3 Hz, 4H), 7.47−7.28 (m, 8H), 5.17 (s, 1H), 4.10−3.99 (m, 1H), 3.96 (br s, 0.5H), 3.76 (dd, J = 10.0, 3.8 Hz, 0.5H), 3.67−3.52 (m, 2H), 3.46 (dd, J = 10.6, 7.0 Hz, 1H), 2.44 (s, 3H), 2.42−2.21 (m, 1.5H), 2.21−2.09 (m, 0.5H), 1.45 (s, 4.5H), 1.31 (s, 4.5H), 1.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.0, 145.0, 135.6, 134.0, 133.9, 133.5, 133.2, 133.1, 133.1, 130.1, 129.9, 129.9, 127.9, 80.1, 79.9, 79.4, 65.0, 64.1, 57.2, 52.8, 52.2, 35.7, 34.4, 29.8, 28.6, 28.5, 27.0, 21.8, 19.4, 19.3. HRMS (ESI) calcd for $C_{33}H_{43}NO_6SSi$ (M + Na)+: m/z 632.24726, found: 632.24846 (−1.91 ppm).

*Oxetan-3-yl 4-Methylbenzenesulfonate (**S2**).* A solution of 3-oxetanol (1 g, 13.5 mmol, 1 equiv) and tosyl chloride (5.15 g, 27 mmol, 2 equiv) in dichloromethane (35 mL) was treated at 0 °C by triethylamine (7.5 mL, 54 mmol, 4 equiv). The resulting mixture was allowed to stir overnight at room temperature. Excess tosyl chloride was readily decomposed upon the addition of *N*,*N*-dimethylethylenediamine and stirring for 10 min at room temperature. Water was added to the mixture, and the product was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification on SiO_2 using hexane/EtOAc = 95/5−80/20 led to the isolation of **S2** as a white solid (2.5 g, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81−7.75 (m, 2H), 7.40−7.33 (m, 2H), 5.30 (tt, J = 6.3, 5.5 Hz, 1H), 4.76−4.62 (m, 4H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 133.1, 130.2, 128.0, 77.2, 71.6, 21.8. HRMS (ESI) calcd for $C_{10}H_{12}O_4S$ (M + H)+: m/z 229.05291, found: 229.05292 (0 ppm).

*1-(tert-Butyl) 2-Methyl (2S,4S)-4-(Tosyloxy)pyrrolidine-1,2-dicarboxylate (**S3**).* Tosyl chloride (234 mg, 1.23 mmol, 1.5 equiv) in dichloromethane (1.5 mL) was treated by trimethylamine hydrochloride (7.8 mg, 0.082 mmol, 0.1 equiv) and triethylamine (0.23 mL, 1.64 mmol, 2 equiv) at 0 °C. Then, *N*-Boc-cis-4-hydroxy-L-proline methyl ester (200 mg, 0.82 mmol, 1 equiv) in dichloromethane (0.5 mL) was added at 0 °C. The resulting mixture was stirred overnight. Excess tosyl chloride was readily decomposed upon the addition of *N*,*N*-dimethylethylenediamine and stirring for 10 min at room temperature. Water was added to the mixture, and the product was extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification on SiO_2 using hexane/EtOAc = 90/10−70/30 led to the isolation of **S3** as a white solid (175 mg, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 7.79−7.69 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.08−4.96 (m, 1H), 4.36 (ddd, J = 31.8, 7.8, 4.3 Hz, 1H), 3.66 (s, 3H), 3.64−3.51 (m, 2H), 2.46−2.38 (m, 1H), 2.42 (s, 3H), 2.37−2.28 (m, 1H), 1.40 (d, J = 12.6 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 172.0, 171.7, 153.8, 153.4, 145.2, 133.7, 133.6, 130.4, 130.1, 130.0, 129.3, 127.8, 80.7, 78.9, 77.8, 57.4, 57.1, 52.5, 52.3, 52.2, 51.6, 37.0, 36.1, 28.4, 28.3, 21.8, 14.1. HRMS (ESI) calcd for $C_{18}H_{25}NO_7S$ (M + Na)+: m/z 422.12439, found: 422.12556 (−2.77 ppm).

General Procedure A for the Nickel-Reductive Cross-Coupling Reactions. A sealed tube was charged with the bromo isoquinolone derivative (1 equiv), $NiBr_2$·glyme (0.05 equiv), 4,4′-di-*tert*-butyl 2,2′-dipyridyl (0.05 equiv), potassium iodide (1 equiv), and manganese (2 equiv) and was purged with argon. A solution of tosylate (3 equiv) in DMA (0.2 M with respect to isoquinolone) was then added followed by 4-ethyl pyridine (1 equiv). The tube was sealed, and the resulting mixture was stirred at 80 °C for 18 h. Completion of the reaction was checked by thin-layer chromatography (TLC, hexane/EtOAc = 6/4). After cooling down to room temperature, the mixture was filtered over a pad of celite and rinsed with acetonitrile. After evaporation, the crude was purified over SiO_2 using typically hexane/EtOAc = 8/2 to 6/4 as eluent.

General Procedure B for the Photoredox Cross-Coupling Reactions. (Prepared in the dark) To a 25 mL (16 mm × 150 mm) test tube dried and flushed under argon were added successively bromo isoquinolone (0.250 mmol, 1.0 equiv), carboxylic acid (0.750 mmol, 3.0 equiv), 4,4′-di-*tert*-butyl 2,2′-dipyridyl (10.1 mg, 37.6 μmol, 0.15 equiv), $NiCl_2$·glyme (5.6 mg, 25.1 μmol, 0.1 equiv), (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF_6 (2.8 mg, 2.51 μmol, 0.01 equiv), and Cs_2CO_3 (248 mg). One vacuum/argon cycle was performed, and DMF (12.5 mL) was added. The green suspension was vigorously stirred while being degassed with argon for 20 min. The reaction was then sealed and irradiated with a 40 W blue LED Kessil lamp placed at a distance of 6−8 cm. A fan was placed above to dispel the heat, and the reaction was stirred at rt for 18 h whereby TLC/liquid chromatography−mass spectrometry (LC−MS) analysis indicated that the reaction went to completion. The suspension was transferred to a separatory funnel containing a 1:1 Et_2O/$NaHCO_3$ aq biphasic solution (100 mL) and extracted. The aqueous layer was collected and further extracted ×2 with Et_2O (50 mL). The organic layers were combined, washed ×1 with distilled H_2O (50 mL), ×1 with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residual oil was chromatographed over SiO_2.

*tert-Butyl 4-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-piperidine-1-carboxylate (**3**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **3** as a white solid (60 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 8.3 Hz, 1H), 7.36−7.24 (m, 7H), 7.07 (d, J = 7.4 Hz, 1H), 6.44 (d, J = 7.4 Hz, 1H), 5.20 (s, 2H), 4.27 (s, 2H), 2.92−2.68 (m, 3H), 1.86 (d, J = 12.7 Hz, 2H), 1.67 (qd, J = 12.6, 3.8 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 154.9, 150.4, 137.4, 137.0, 131.6,

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128.9, 128.5, 128.0, 127.9, 126.4, 124.9, 123.6, 106.5, 79.6, 51.7, 44.2, 43.0, 33.0, 28.6. HRMS (ESI) calcd for $C_{26}H_{30}N_2O_3$ (M + H)+: m/z 419.23292, found: 419.23466 (4.16 ppm).

*tert-Butyl 3-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-piperidine-1-carboxylate (**5**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **5** as a white solid (28 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 8.3 Hz, 1H), 7.39−7.27 (m, 7H), 7.07 (d, J = 7.4 Hz, 1H), 6.44 (d, J = 7.4 Hz, 1H), 5.21 (s, 2H), 4.33−4.01 (m, 2H), 2.96−2.60 (m, 3H), 2.06 (d, J = 12.7 Hz, 1H), 1.83−1.55 (m, 3H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 154.9, 148.2, 137.4, 137.1, 131.7, 128.9, 128.5, 128.1, 127.9, 126.5, 125.0, 124.2, 106.5, 79.8, 51.7, 50.3, 44.2, 42.8, 31.7, 28.6, 25.4. HRMS (ESI) calcd for $C_{26}H_{30}N_2O_3$ (M + H)+: m/z 419.23292, found: 419.23277 (0.36 ppm).

*tert-Butyl 3-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-piperidine-1-carboxylate (**6**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **6** as a white solid (23 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 8.1 Hz, 1H), 7.40−7.29 (m, 2H), 7.05 (d, J = 7.3 Hz, 1H), 6.44 (d, J = 7.3 Hz, 1H), 4.36−4.04 (m, 2H), 3.59 (s, 3H), 2.88−2.71 (m, 2H), 2.12−2.01 (m, 1H), 1.84−1.54 (m, 4H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 154.9, 148.0, 137.5, 132.8, 128.0, 126.4, 124.9, 124.1, 106.1, 79.8, 67.8, 59.6, 58.7, 50.2, 45.9, 44.3, 42.8, 37.1, 31.7, 30.9, 29.8, 28.6, 25.5. HRMS (ESI) calcd for $C_{20}H_{26}N_2O_3$ (M + Na)+: m/z 365.18356, found: 365.18376 (−0.53 ppm).

*tert-Butyl 3-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-pyrrolidine-1-carboxylate (**7**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **7** as a white solid (48 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 8.3 Hz, 1H), 7.38−7.35 (m, 1H), 7.34−7.25 (m, 6H), 7.08 (d, J = 7.3 Hz, 1H), 6.44 (d, J = 7.1 Hz, 1H), 5.21 (s, 2H), 3.91−3.78 (m, 1H), 3.61 (dt, J = 47.7, 8.2 Hz, 1H), 3.51−3.29 (m, 3H), 2.36−2.26 (m, 1H), 2.09−1.97 (m, 1H), 1.48 (d, J = 5.2 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 154.6, 146.3, 146.3, 137.4, 137.0, 131.8, 128.9, 128.6, 128.0, 127.9, 126.4, 125.2, 124.0, 106.4, 79.5, 52.4, 51.7, 51.6, 46.0, 45.7, 44.4, 43.5, 33.4, 32.4, 28.7. HRMS (ESI) calcd for $C_{25}H_{28}N_2O_3$ (M + Na)+: m/z 427.19921, found: 427.19922 (−0.02 ppm).

*tert-Butyl 3-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-pyrrolidine-1-carboxylate (**8**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **8** as a white solid (50 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 8.35 (d, J = 8.2 Hz, 1H), 7.36−7.30 (m, 2H), 7.05 (d, J = 7.1 Hz, 1H), 6.43 (d, J = 6.9 Hz, 1H), 3.90−3.78 (m, J = 22.6, 14.5 Hz, 1H), 3.68−3.62 (m, 0.6H), 3.57 (s, 3H), 3.56−3.52 (m, 0.4H), 3.49−3.36 (m, 2.4H), 3.36−3.30 (m, 0.6H), 2.36−2.24 (m, J = 4.1 Hz, 1H), 2.08−1.98 (m, 1H), 1.47 (d, J = 5.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 162.50, 154.59, 146.07, 145.98, 137.52, 132.90, 128.20, 126.26, 124.97, 123.94, 105.94, 79.53, 52.35, 51.64, 45.96, 45.67, 44.40, 43.46, 37.08, 33.35, 32.40, 28.64, 28.13. HRMS (ESI) calcd for $C_{19}H_{24}N_2O_3$ (M + H)+: m/z 329.18597, found: 329.18645 (−1.46 ppm).

*tert-Butyl 3-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-azetidine-1-carboxylate (**9a**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **9a** as a thick pale oil (31 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 8.3 Hz, 1H), 7.44 (dd, J = 12.2, 3.9 Hz, 2H), 7.35−7.26 (m, 5H), 7.10 (d, J = 7.4 Hz, 1H), 6.46 (d, J = 7.4 Hz, 1H), 5.21 (s, 2H), 4.38 (t, J = 8.7 Hz, 2H), 4.05−3.98 (m, 2H), 3.87−3.79 (m, 1H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 156.5, 146.9, 137.5, 137.0, 132.0, 128.9, 128.9, 128.1, 128.0, 125.9, 125.3, 123.9, 106.3, 79.9, 56.4, 51.8, 33.7, 28.5. HRMS (ESI) calcd for $C_{24}H_{26}N_2O_3$ (M + H)+: m/z 391.20162, found: 391.20128 (0.86 ppm).

*6-(1-Acryloylazetidin-3-yl)-2-benzylisoquinolin-1(2H)-one (**9b**).* **9a** (30 mg, 0.077 mmol, 1 equiv) was treated by a 4 M solution of HCl.dioxane (0.4 mL, 1.54 mmol, 20 equiv) at room temperature for 2 h under argon. After complete evaporation of the solvent, the residue was taken up in dichloromethane (0.8 mL) and subsequently treated by triethylamine (22 μL, 0.154 mmol, 2 equiv) and acryloyl chloride (30 μL, 0.385 mmol, 5 equiv). The resulting mixture was allowed to stir at room temperature for 18 h. The reaction was quenched upon the addition of an excess 1 M NaOH aqueous solution. The product was extracted with ethyl acetate, and the organic phase was washed with brine and dried over Na_2SO_4. Purification on SiO_2 using hexane/EtOAc = 7/3−4/6 as eluent furnished product **9b** (19 mg) in a 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 8.8 Hz, 1H), 7.46−7.40 (m, 2H), 7.37−7.26 (m, 5H), 7.11 (d, J = 7.4 Hz, 1H), 6.46 (d, J = 7.4 Hz, 1H), 6.39 (dd, J = 17.0, 2.0 Hz, 1H), 6.24 (dd, J = 17.0, 10.1 Hz, 1H), 5.71 (dd, J = 10.2, 2.0 Hz, 1H), 5.22 (s, 2H), 4.68 (t, J = 8.7 Hz, 1H), 4.54 (t, J = 9.6 Hz, 1H), 4.33−4.17 (m, 2H), 3.97 (ddd, J = 8.8, 7.4, 4.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 162.1, 146.1, 137.6, 136.9, 132.2, 129.1, 129.0, 128.1, 128.0, 127.9, 125.8, 125.7, 125.5, 123.8, 106.3, 57.4, 54.9, 51.8, 33.7. HRMS (ESI) calcd for $C_{22}H_{20}N_2O_2$ (M + H)+: m/z 345.15975, found: 345.16108 (−3.85 ppm).

*2-Benzyl-6-(tetrahydro-2H-pyran-4-yl)isoquinolin-1(2H)-one (**11**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **11** as a white solid (39 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 8.3 Hz, 1H), 7.37 (dd, J = 8.4, 1.7 Hz, 1H), 7.34−7.25 (m, 6H), 7.08 (d, J = 7.4 Hz, 1H), 6.46 (d, J = 7.2 Hz, 1H), 5.22 (s, 2H), 4.16−4.06 (m, 2H), 3.55 (td, J = 11.5, 2.9 Hz, 2H), 2.95−2.81 (m, 1H), 1.97−1.77 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 150.5, 137.5, 137.1, 131.6, 128.9, 128.5, 128.0, 127.9, 126.4, 124.9, 123.6, 106.6, 68.4, 51.7, 41.9, 33.7. HRMS (ESI) calcd for $C_{21}H_{21}NO_2$ (M + H)+: m/z 320.16451, found: 320.1651 (−1.86 ppm).

*2-Benzyl-6-(tetrahydrofuran-3-yl)isoquinolin-1(2H)-one (**12**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **12** as a white solid (31 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 8.2 Hz, 1H), 7.42−7.25 (m, 7H), 7.08 (d, J = 7.4 Hz, 1H), 6.44 (d, J = 7.3 Hz, 1H), 5.21 (s, 2H), 4.20−4.05 (m, 2H), 3.99−3.89 (m, 1H), 3.82 (dd, J = 8.6, 6.9 Hz, 1H), 3.58−3.45 (m, 1H), 2.49−2.36 (m, 1H), 2.05 (ddd, J = 15.7, 12.4, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 147.9, 137.4, 137.0, 131.8, 128.9, 128.7, 128.0, 127.9, 126.6, 125.0, 124.2, 106.4, 74.6, 68.6, 51.7, 45.2, 34.8. HRMS (ESI) calcd for $C_{20}H_{19}NO_2$ (M + H)+: m/z 306.14886, found: 306.14915 (−0.96 ppm).

*1-(tert-Butyl) 2-Methyl (2S,4S)-4-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)pyrrolidine-1,2-dicarboxylate (**13**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **13** as a white

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solid (65 mg, 88%). dr = 8/2 ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.40 (d, J = 8.2 Hz, 1H), 7.39−7.22 (m, 7H), 7.08 (d, J = 7.4 Hz, 1H), 6.42 (dd, J = 7.4, 2.0 Hz, 1H), 5.20 (s, 2H), 4.58−4.51 (m, 0.4H), 4.42 (t, J = 5.6 Hz, 0.6H), 4.05 (ddd, J = 19.9, 8.9, 6.3 Hz, 1H), 3.76 (s, 3H), 3.74−3.39 (m, 3H), 2.43−2.35 (m, 1H), 1.45 (d, J = 10.4 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 173.4, 173.2, 162.1, 154.3, 153.7, 145.1, 137.4, 137.0, 132.0, 128.9, 128.8, 128.0, 128.0, 126.1, 125.4, 124.2, 106.3, 80.4, 59.2, 58.9, 52.9, 52.4, 52.3, 52.2, 51.8, 42.6, 41.7, 37.8, 36.8, 28.5, 28.4, 22.4, 14.2. HRMS (ESI) calcd for $C_{27}H_{30}N_2O_5$ (M + H)+: m/z 463.22275, found: 463.22276 (−0.02 ppm).

*di-tert-Butyl (2S,4S)-4-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)pyrrolidine-1,2-dicarboxylate (**14**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **14** as a white solid (60 mg, 75%). dr = 8/2. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.40 (d, J = 8.3 Hz, 1H), 7.37−7.27 (m, 7H), 7.08 (d, J = 7.4 Hz, 1H), 6.43 (dd, J = 7.3, 4.3 Hz, 1H), 5.20 (s, 2H), 4.44−4.39 (m, 0.3H), 4.30 (dd, J = 7.5, 3.4 Hz, 0.7H), 4.10−3.95 (m, 1H), 3.71−3.56 (m, 1H), 3.54−3.35 (m, 1H), 2.37 (dt, J = 11.9, 8.4 Hz, 2H), 1.49 (d, J = 4.0 Hz, 9H), 1.46 (d, J = 3.5 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 172.0, 162.1, 154.2, 153.9, 145.5, 137.4, 137.0, 131.9, 128.9, 128.8, 128.0, 128.0, 126.3, 126.2, 125.3, 124.3, 124.2, 106.4, 81.5, 81.4, 80.2, 80.1, 60.0, 59.9, 53.0, 52.3, 51.8, 43.8, 42.9, 42.6, 41.6, 38.3, 37.9, 37.3, 36.8, 28.5, 28.5, 28.2. HRMS (ESI) calcd for $C_{30}H_{36}N_2O_5$ (M + H)+: m/z 505.2697, found: 505.26909 (1.2 ppm).

*tert-Butyl (2S,4S)-4-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-2-(((tert-butyldiphenylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (**15**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **15** as a white solid (84 mg, 79%). dr = 9/1. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 8.44 (d, J = 8.3 Hz, 1H), 7.70 (s, 4H), 7.48−7.27 (m, 13H), 7.10 (d, J = 7.4 Hz, 1H), 6.46 (d, J = 7.3 Hz, 1H), 5.23 (s, 2H), 4.28−4.16 (m, 0.5H), 4.10−4.03 (m, 0.5H), 4.02−3.61 (m, 4H), 3.54 (t, J = 10.0 Hz, 0.5H), 3.39 (t, J = 9.8 Hz, 0.5H), 2.60−2.50 (m, J = 11.9, 6.5 Hz, 0.5H), 2.47−2.37 (m, J = 11.7, 6.7 Hz, 0.5H), 2.31−2.07 (m, 1H), 1.49 (s, 4H), 1.39 (s, 5H), 1.11 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 162.1, 154.4, 146.8, 146.7, 145.8, 137.4, 137.0, 135.7, 133.7, 133.7, 133.6, 133.4, 131.8, 129.9, 129.8, 128.9, 128.6, 128.0, 127.9, 127.9, 126.6, 126.4, 125.2, 125.1, 124.4, 124.1, 106.4, 79.7, 79.5, 64.8, 64.6, 58.8, 53.6, 52.8, 51.7, 42.6, 41.5, 36.5, 35.5, 28.6, 28.5, 27.0, 19.4. HRMS (ESI) calcd for $C_{42}H_{48}N_2O_4Si$ (M + Na)+: m/z 695.32756, found: 695.32909 (−2.21 ppm).

*tert-Butyl (2R,4S)-4-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-2-methylpyrrolidine-1-carboxylate (**16**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **16** as a white solid (47 mg, 71%). dr = 8/2. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.41 (d, J = 8.3 Hz, 1H), 7.41−7.26 (m, 7H), 7.09 (d, J = 7.4 Hz, 1H), 6.45 (dd, J = 7.3, 2.8 Hz, 1H), 5.22 (s, 2H), 4.25−3.74 (m, 2H), 3.68−3.23 (m, 2H), 2.65−2.49 (m, 0.2H), 2.31−2.13 (m, 0.8H), 2.01 (br s, 0.8H), 1.84−1.64 (m, 0.2H), 1.47 (s, 9H), 1.31 (br s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 162.2, 146.4, 145.6, 137.4, 137.3, 137.0, 131.8, 128.9, 128.6, 128.5, 128.0, 127.9, 126.4, 126.4, 125.1, 124.2, 124.1, 106.4, 79.4, 53.2, 51.7, 41.2, 40.8, 39.7, 28.7, 21.1. HRMS (ESI) calcd for $C_{26}H_{30}N_2O_3$ (M + H)+: m/z 419.23292, found: 419.23421 (−3.08 ppm).

*tert-Butyl (3S,4R)-3-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-4-vinylpyrrolidine-1-carboxylate (**17**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **17** as a white solid (29 mg, 44%). dr = 97/3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 8.1 Hz, 1H), 7.40−7.25 (m, 7H), 7.08 (d, J = 7.1 Hz, 1H), 6.44 (d, J = 7.0 Hz, 1H), 5.66 (ddd, J = 17.6, 10.3, 7.6 Hz, 1H), 5.20 (s, 2H), 5.03−4.87 (m, 2H), 3.97−3.72 (m, 2H), 3.44 (dt, J = 33.6, 10.7 Hz, 1H), 3.33−3.11 (m, 2H), 2.98 (dt, J = 18.1, 9.0 Hz, 1H), 1.48 (d, J = 12.0 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 154.4, 154.4, 144.3, 144.2, 137.4, 137.0, 136.3, 136.2, 131.8, 128.9, 128.7, 128.1, 128.0, 126.7, 125.4, 125.1, 117.5, 106.4, 79.7, 53.2, 52.5, 51.8, 51.3, 50.9, 50.8, 50.4, 50.0, 49.2, 28.6. HRMS (ESI) calcd for $C_{27}H_{30}N_2O_3$ (M + H)+: m/z 431.23292, found: 431.23474 (−4.23 ppm).

*2-Benzyl-6-((3aR,5S,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)isoquinolin-1(2H)-one (**18**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **18** as a white solid (10 mg, 13%). dr > 99/1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.36 (s, 1H), 7.34−7.27 (m, 5H), 7.08−7.04 (m, J = 7.4 Hz, 1H), 6.43 (d, J = 7.4 Hz, 1H), 6.01 (d, J = 3.7 Hz, 1H), 5.21 (s, 2H), 4.58 (d, J = 3.7 Hz, 1H), 4.32 (dd, J = 7.2, 3.9 Hz, 1H), 4.23 (d, J = 3.9 Hz, 1H), 3.80−3.72 (m, 1H), 3.15 (dd, J = 14.5, 2.5 Hz, 1H), 2.92 (dd, J = 14.4, 9.9 Hz, 1H), 1.50 (s, 3H), 1.33 (d, J = 5.3 Hz, 6H), 1.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 143.3, 137.2, 137.1, 131.4, 129.0, 128.6, 128.2, 128.1, 128.0, 126.3, 124.9, 112.4, 106.6, 106.5, 101.1, 84.3, 83.3, 75.1, 72.6, 51.8, 39.9, 27.4, 26.7, 24.1, 23.9. HRMS (ESI) calcd for $C_{28}H_{31}NO_6$ (M + H)+: m/z 478.22241, found: 478.22368 (−2.64 ppm).

*Methyl (S)-3-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-2-((tert-butoxycarbonyl)amino)propanoate (**19**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **19** as a white solid (26 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 8.0 Hz, 1H), 7.36−7.22 (m, 7H), 7.08 (d, J = 7.4 Hz, 1H), 6.42 (d, J = 7.3 Hz, 1H), 5.21 (s, 2H), 5.02 (d, J = 8.2 Hz, 1H), 4.64 (dd, J = 13.7, 6.4 Hz, 1H), 3.71 (s, 3H), 3.20 (qd, J = 13.7, 6.0 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 173.0, 172.2, 162.2, 155.5, 155.1, 141.0, 137.3, 137.0, 131.8, 129.0, 128.5, 128.4, 128.1, 128.0, 126.5, 125.4, 106.4, 54.4, 52.6, 52.5, 51.8, 38.6, 29.0, 28.4. HRMS (ESI) calcd for $C_{25}H_{28}N_2O_5$ (M + H)+: m/z 437.2071, found: 437.20645 (1.48 ppm).

*Methyl (2S)-3-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-2-((tert-butoxycarbonyl)amino)butanoate (**20**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **20** as a white solid (31 mg, 43%). dr = 1/1. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.39 (d, J = 8.8 Hz, 1H), 7.37−7.22 (m, 7H), 7.08 (d, J = 7.4 Hz, 1H), 6.45 (d, J = 7.3 Hz, 1H), 5.21 (s, 2H), 5.12 (d, J = 9.3 Hz, 0.45H), 4.86 (d, J = 8.9 Hz, 0.55H), 4.58 (dd, J = 15.3, 9.2 Hz, 1H), 3.68 (s, 1.65H), 3.57 (s, 1.35H), 3.51−3.39 (m, 0.45H), 3.32 (p, J = 7.0 Hz, 0.55H), 1.48−1.31 (m, 3H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 172.1, 172.1, 166.1, 162.2, 155.6, 155.3, 146.5, 145.9, 137.3, 137.2, 137.0, 137.0, 131.8, 131.7, 129.0, 128.9, 128.6, 128.4, 128.1, 128.0, 127.9, 126.8, 125.5, 125.4, 124.9, 124.9, 106.5, 106.5, 80.2, 67.9, 58.8, 58.7, 52.3, 51.8, 43.0, 42.5, 39.0, 30.7, 29.8, 29.1, 28.4, 24.1, 23.1,

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17.4, 16.5, 14.2, 11.2. HRMS (ESI) calcd for $C_{26}H_{30}N_2O_5$ (M + H)+: m/z 451.22275, found: 451.22332 (−1.27 ppm).

*tert-Butyl 4-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-piperidine-1-carboxylate (**21**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (8:2 hexane/EtOAc) to afford **21** as a white solid (40 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27−8.22 (m, J = 1.0 Hz, 1H), 7.49−7.42 (m, 2H), 7.02 (d, J = 7.3 Hz, 1H), 6.45 (d, J = 7.3 Hz, 1H), 4.25 (br s, 2H), 3.58 (s, 3H), 2.92−2.74 (m, 3H), 1.85 (d, J = 13.0 Hz, 2H), 1.68 (ddd, J = 25.6, 12.5, 4.4 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 154.9, 144.8, 135.7, 132.0, 131.3, 126.3, 125.4, 105.9, 79.6, 44.4, 42.8, 37.2, 33.2, 28.6. HRMS (ESI) calcd for $C_{20}H_{26}N_2O_3$ (M + Na)+: m/z 365.18356, found: 365.18458 (−2.77 ppm).

*2-Methyl-7-(tetrahydro-2H-pyran-4-yl)isoquinolin-1(2H)-one (**22**).* Following general procedure A, the crude oil was chromatographed over SiO_2 (8:2 hexane/EtOAc) to afford **22** as a white solid (30 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 1.3 Hz, 1H), 7.49 (dt, J = 19.2, 5.0 Hz, 2H), 7.03 (d, J = 7.3 Hz, 1H), 6.46 (d, J = 7.3 Hz, 1H), 4.13−4.06 (m, 2H), 3.59 (s, 3H), 3.55 (td, J = 11.7, 2.2 Hz, 2H), 2.90 (tt, J = 11.9, 3.9 Hz, 1H), 1.89 (dtd, J = 16.2, 11.9, 4.4 Hz, 2H), 1.81 (ddd, J = 7.9, 4.6, 2.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 144.9, 135.7, 132.0, 131.2, 126.3, 125.4, 105.9, 68.4, 41.7, 37.2, 33.9. HRMS (ESI) calcd for $C_{15}H_{17}NO_2$ (M + H)+: m/z 244.13321, found: 244.13391 (−2.89 ppm).

*tert-Butyl 2-(1-Oxo-1,2-dihydroisoquinolin-6-yl)-pyrrolidine-1-carboxylate (**27**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford **27** as a white foam (53 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 11.72 (m, 1H), 8.35 (m, 1H), 7.35−7.27 (m, 2H), 7.22−7.09 (m, 1H), 6.51 (m, 1H), 5.12−4.82 (m, 1H), 3.65 (m, 2H), 2.38 (m, 1H), 2.03−1.77 (m, 3H), 1.45 (s, 3H), 1.13 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 164.5, 154.6, 150.3, 149.3, 138.4, 128.2, 128.0, 127.8, 127.5, 124.8, 124.7, 124.4, 122.7, 106.9, 106.7, 79.7, 61.4, 61.0, 47.6, 47.3, 36.0, 34.9, 28.6, 28.5, 28.2, 23.8, 23.4. HRMS (ESI) calcd for $C_{18}H_{22}N_2O_3$ (M + H)$^+$: m/z 315.17032, found 315.16986.

*tert-Butyl (2S,4R)-4-Hydroxy-2-(1-oxo-1,2-dihydroisoquinolin-6-yl)pyrrolidine-1-carboxylate (**28**).* Following general procedure B, the crude oil was transferred in a one-neck round-bottomed flask dried and flushed under argon. THF (2.5 mL) was added, and the yellow solution was cooled to 0 °C, whereby tetra-*n*-butylammonium fluoride (TBAF, 300 μL, C = 1.0 M in THF, 0.3 mmol, 1.2 equiv) was added. Stirred at 0 °C for 5 min and then for 3h at rt, whereby LC−MS analysis indicated that the reaction went to completion. The reaction was quenched with a saturated aq $NaHCO_3$ solution (5.0 mL), and the aqueous layer was extracted ×3 with EtOAc (5.0 mL). The organic layers were combined, washed ×1 with distilled H_2O (5.0 mL), ×1 with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude oil was chromatographed over SiO_2 (97:3 $CHCl_3$/MeOH) to afford **28** as a white solid (22 mg, 27% over two steps). dr = 85:15. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 10.97 (m, 1H), 8.34 (m, 1H), 7.48−7.30 (m, 2H), 7.12 (m, 1H), 6.50 (m, 1H), 5.23−4.89 (m, 1H), 4.52 (m, 1H), 3.98−3.55 (m, 2H), 2.71−2.16 (m, 2H), 2.05 (m, 0.15H) 1.99 (m, 0.85H), 1.44 (m, 3H), 1.10 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 164.1, 155.0, 150.1, 138.4, 128.1, 127.9, 125.0, 124.6, 123.0, 106.7, 80.1, 70.2, 69.7, 60.4, 56.1, 45.2, 28.6, 28.2. HRMS (ESI) calcd for $C_{18}H_{22}N_2O_4$ (M + H)$^+$: m/z 331.16523, found 331.16679.

*tert-Butyl 2-(1-Oxo-1,2-dihydroisoquinolin-6-yl)indoline-1-carboxylate (**29**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (96:4 $CHCl_3$/MeOH) to afford **29** as a beige solid (29 mg, 32%). ^{1}H NMR (700 MHz, $CDCl_3$, mixture of rotamers) δ 10.66 (br s, 1H), 8.35 (d, J = 8.3 Hz, 1H), 7.42−7.28 (m, 2H), 7.17−7.09 (m, 2H), 7.01 (td, J = 7.5, 1.0 Hz, 1H), 6.47 (d, J = 7.1 Hz, 1H), 5.49 (br s, 1H), 3.79−3.65 (m, 1H), 3.06−2.89 (m, 1H), 1.27 (m, 9H). ^{13}C NMR (176 MHz, $CDCl_3$, mixture of rotamers) δ 163.9, 152.4, 149.7, 143.3, 138.5, 128.3, 128.0, 127.9, 125.4, 125.0, 124.4, 123.0, 122.5, 114.9, 106.8, 81.2, 62.6, 37.8, 28.3. HRMS (ESI) calcd for $C_{22}H_{22}N_2O_3$ (M + H)$^+$: m/z 363.17032, found 363.17178; calcd for $C_{22}H_{22}N_2O_3$ (M + Na)$^+$ 385.15226, found 385.15465.

*tert-Butyl 2-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-indoline-1-carboxylate (**30**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (8:2 Hex/EtOAc) to afford **30** as a pale yellow oil (50 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 8.40 (d, J = 8.3 Hz, 1H), 7.36−7.23 (m, 8H), 7.13 (dd, J = 7.4, 1.4 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.00 (td, J = 7.4, 1.1 Hz, 1H), 6.40 (d, J = 7.4 Hz, 1H), 5.48 (br s, 1H), 5.20 (s, 2H), 3.73 (ddt, J = 16.2, 10.7, 1.1 Hz, 1H), 2.96 (dd, J = 16.4, 3.7 Hz, 1H), 1.59−1.11 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 162.2, 152.4, 149.2, 143.1, 137.4, 137.0, 131.8, 128.9, 128.2, 128.0, 128.0, 125.5, 125.0, 124.5, 122.9, 122.1, 114.9, 106.5, 81.2, 62.5, 51.8, 37.8, 28.3. HRMS (ESI) calcd for $C_{14}H_{23}NO_4$ (M + Na)$^+$: m/z 292.15193, found 292.15222.

*tert-Butyl 2-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-pyrrolidine-1-carboxylate (**31a**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (7:3 hexane/EtOAc) to afford **31a** as a colorless oil (68 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 8.40 (d, J = 8.3 Hz, 1H), 7.36−7.28 (m, 7H), 7.18−6.95 (m, 1H), 6.44 (d, J = 7.4 Hz, 1H), 5.21 (s, 2H), 4.95 (m, 1H), 3.62 (m, 2H), 2.37 (br s, 1H), 1.89 (m, 3H), 1.45 (s, 3H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 162.3, 154.7, 149.9, 137.2, 137.1, 131.7, 128.9, 128.7, 128.4, 128.2, 128.0, 125.2, 124.9, 124.6, 122.3, 106.8, 106.5, 79.7, 61.4, 61.0, 51.8, 47.7, 47.3, 36.0, 28.6, 28.3, 28.2, 23.8, 23.4. HRMS (ESI) calcd for $C_{25}H_{28}N_2O_3$ (M + H)$^+$: m/z 405.21727, found 405.21879; calcd for $C_{25}H_{28}N_2O_3$ (M + Na)$^+$: m/z 427.19921, found 427.19996.

*tert-Butyl 2-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-piperidine-1-carboxylate (**32**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (8:2 hexane/EtOAc) to afford **32** as a pale yellow oil (28 mg, 27% (33% conversion)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 8.5 Hz, 1H), 7.38−7.27 (m, 7H), 7.08 (d, J = 7.3 Hz, 1H), 6.45 (dd, J = 7.4, 0.6 Hz, 1H), 5.48 (m, 1H), 5.22 (s, 2H), 4.16−4.02 (m, 1H), 2.80 (ddd, J = 13.5, 11.9, 4.0 Hz, 1H), 2.35 (dd, J = 14.1, 3.4 Hz, 1H), 1.95 (m, 1H), 1.63−1.56 (m, 2H), 1.45 (s, 10H), 1.42−1.32 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5, 156.0, 146.0, 137.6, 137.3, 131.9, 129.2, 128.9, 128.4, 128.2, 125.9, 125.2, 124.0, 106.9, 80.3, 54.0, 52.0, 40.8, 28.8, 28.7, 25.7, 19.8. HRMS (ESI) calcd for $C_{26}H_{30}N_2O_3$ (M + H)$^+$: m/z 419.23292, found 419.23371; calcd for $C_{26}H_{30}N_2O_3$ (M + Na)$^+$: m/z 441.21486, found 441.21490.

*tert-Butyl 2-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-pyrrolidine-1-carboxylate (**33**).* Following general procedure

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B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford **33** as a pale green solid (60 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 8.35 (d, J = 8.3 Hz, 1H), 7.29 (m, 2H), 7.05 (m, 1H), 6.42 (d, J = 7.3 Hz, 1H), 5.10−4.78 (m, 1H), 3.62 (m, 5H), 2.45−2.24 (m, 1H), 1.88 (m, 3H), 1.45 (s, 3H), 1.12 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 162.6, 154.6, 149.7, 148.7, 137.3, 132.8, 132.6, 128.2, 128.0, 124.9, 124.8, 122.5, 122.3, 106.3, 106.0, 79.6, 61.4, 60.9, 47.6, 47.3, 37.1, 36.0, 34.9, 28.6, 28.2, 23.8, 23.4. HRMS (ESI) calcd for $C_{19}H_{24}N_2O_3$ $(M + H)^+$: m/z 329.18597, found 329.18729; calcd for $C_{19}H_{24}N_2O_3$ $(M + Na)^+$: m/z 351.16791, found 351.16882.

*tert-Butyl 2-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-azetidine-1-carboxylate (**34**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford **34** as a yellow oil (60 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 8.3 Hz, 1H), 7.51−7.39 (m, 2H), 7.06 (d, J = 7.3 Hz, 1H), 6.46 (d, J = 7.3 Hz, 1H), 5.28 (t, J = 7.7 Hz, 1H), 4.03 (m, 2H), 3.59 (s, 3H), 2.67 (m, 1H), 2.24−2.07 (m, 1H), 1.51−1.15 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6, 156.7, 146.8, 137.5, 132.8, 128.2, 125.4, 124.6, 122.9, 106.2, 79.9, 64.0, 46.6, 37.1, 28.4, 25.4. HRMS (ESI) calcd for $C_{18}H_{22}N_2O_3$ $(M + H)^+$: m/z 315.17032, found 315.17152; $C_{18}H_{22}N_2O_3$ $(M + Na)^+$: m/z 337.15226, found 337.15313.

*2-Methyl-6-(tetrahydrofuran-2-yl)isoquinolin-1(2H)-one (**35**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford **35** as a yellow solid (28 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 8.3 Hz, 1H), 7.55−7.44 (br s, 1H), 7.41 (dd, J = 8.3, 1.6 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.47 (d, J = 7.3 Hz, 1H), 5.01 (t, J = 7.2 Hz, 1H), 4.14 (dt, J = 8.3, 6.8 Hz, 1H), 3.99 (dt, J = 8.2, 6.9 Hz, 1H), 3.59 (s, 3H), 2.40 (dq, J = 13.2, 6.7 Hz, 1H), 2.13−1.95 (m, 2H), 1.82 (dq, J = 12.2, 7.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 148.1, 137.4, 132.7, 128.0, 125.3, 124.6, 122.3, 106.2, 80.4, 69.1, 37.1, 34.8, 26.1. HRMS (ESI) calcd for $C_{14}H_{15}NO_2$ $(M + H)^+$: m/z 230.11756, found 230.11731; calcd for $C_{14}H_{15}NO_2$ $(M + Na)^+$: m/z 252.09950, found 252.09903.

*tert-Butyl 2-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-6-yl)-5-oxopyrrolidine-1-carboxylate (**36**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (100 EtOAc) to afford **36** as a pale yellow solid (14 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.9, 1H), 7.33 (m, 2H), 7.10 (d, J = 7.3 Hz, 1H), 6.51−6.35 (m, 1H), 5.25 (dd, J = 8.1, 3.9 Hz, 1H), 3.61 (s, 3H), 2.82−2.43 (m, 3H), 1.99−1.85 (m, 1H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 162.4, 149.5, 146.9, 137.7, 133.4, 128.9, 125.7, 124.2, 121.7, 105.8, 83.4, 61.5, 37.2, 31.3, 27.8, 27.2. HRMS (ESI) calcd for $C_{19}H_{22}N_2O_4$ $(M + H)^+$: m/z 343.16523, found 343.16598.

*tert-Butyl (1-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-6-yl)ethyl)carbamate (**38**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford **38** as a pale yellow oil (56 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 8.8 Hz, 1H), 7.41 (m, 2H), 7.05 (d, J = 7.3 Hz, 1H), 6.44 (d, J = 7.3 Hz, 1H), 4.92 (m, 2H), 3.58 (s, 3H), 1.55−1.33 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5, 155.2, 148.6, 137.5, 132.8, 128.3, 125.3, 124.8, 123.0, 106.1, 79.8, 50.3, 37.1, 28.5, 22.8. HRMS (ESI) calcd for $C_{17}H_{22}N_2O_3$ $(M + H)^+$: m/z: 303.17032, found 303.17065; calcd for $C_{17}H_{22}N_2O_3$ $(M + Na)^+$: m/z 325.15226, found 325.15258.

*6-((Benzyloxy)methyl)-2-methylisoquinolin-1(2H)-one (**39**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford **39** as a yellow oil (54 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (m, 1H), 7.54−7.51 (m, 1H), 7.49 (m, 1H), 7.42−7.28 (m, 4H), 7.06 (d, J = 7.3 Hz, 1H), 6.48 (m, 1H), 4.67 (s, 2H), 4.62 (s, 2H), 3.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6, 142.8, 138.0, 137.4, 132.8, 132.5, 132.1, 128.6, 128.0, 127.9, 127.8, 126.9, 126.1, 126.0, 125.6, 124.3, 106.1, 106.1, 72.7, 71.7, 37.1, 37.1. HRMS (ESI) calcd for $C_{18}H_{17}NO_2$ $(M + H)^+$: m/z 280.13321, found 280.13461; calcd for $C_{18}H_{17}NO_2$ $(M + Na)^+$: m/z 302.11515, found 302.11662.

*tert-Butyl 2-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-pyrrolidine-1-carboxylate (**40**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford **40** as a yellow oil (60 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 8.27 (br s, 1H), 7.48 (br s, 2H), 7.06 (m, 1H), 6.50 (m, 1H), 5.16−4.85 (m, 1H), 3.74−3.51 (m, 5H), 2.47−2.27 (m, 1H), 1.89 (m, 3H), 1.48 (br s, 4H), 1.18 (br s, 5H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers) δ 162.7, 154.7, 144.3, 143.4, 135.9, 132.1, 130.2, 129.6, 126.2, 126.0, 124.7, 123.9, 105.9, 79.5, 61.4, 60.8, 47.5, 47.3, 37.2, 36.3, 35.0, 28.7, 28.3, 23.6, 23.5. HRMS (ESI) calcd for $C_{19}H_{24}N_2O_3$ $(M + Na)^+$: m/z 351.16791, found 351.16775; calcd for $C_{19}H_{24}N_2O_3$ $(M+K)^+$: m/z 367.14185, found 367.14163.

*tert-Butyl 2-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-azetidine-1-carboxylate (**41**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford **41** as a yellow oil (46 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.68 (dd, J = 8.2, 1.9 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 6.48 (d, J = 7.3 Hz, 1H), 5.32 (dd, J = 8.8, 6.3 Hz, 1H), 4.03 (t, J = 8.4 Hz, 2H), 3.61 (s, 3H), 2.71−2.56 (m, 1H), 2.17 (m, 1H), 1.29 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 156.7, 141.6, 136.5, 132.4, 130.1, 126.3, 105.9, 79.7, 64.1, 46.7, 37.2, 28.4, 25.6. HRMS (ESI) calcd for $C_{18}H_{22}N_2O_3$ $(M + Na)^+$: m/z 337.15226, found 337.15131; calcd for $C_{18}H_{22}N_2O_3$ $(M +K)^+$: m/z 353.12620, found 353.12973.

*tert-Butyl 2-(2-Methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-indoline-1-carboxylate (**42**).* Following general procedure B, the crude oil was chromatographed over SiO_2 (5:5 hexane/EtOAc) to afford **42** as a yellow oil (62 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers, mixture with 2-methylisoquinolin-1(2*H*)-one (**S4**)) δ 8.43 (d, J = 8.1 Hz, 0.35H, **S4**), 8.30 (s, 1H), 7.62 (ddd, J = 8.2, 7.1, 1.4 Hz, 0.35H, **S4**), 7.53−7.44 (m, 0.70H, **S4**), 7.42 (m, 2H), 7.26−7.21 (t, J = 9.2 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.06 (d, J = 7.3 Hz, 0.35H, **S4**), 7.03 (d, J = 7.3 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.48 (d, J = 7.3 Hz, 0.35H, **S4**), 6.44 (d, J = 7.2 Hz, 1H), 5.52 (br s, 1H), 3.72 (dd, J = 16.3, 10.7 Hz, 1H), 3.59 (d, J = 8.0 Hz, 4H), 2.97 (dd, J = 16.4, 3.7 Hz, 1H), 1.46−1.20 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers, mixture with **S4**) δ 162.7 (**S4**), 162.6, 152.4, 143.5, 143.1, 137.3 (**S4**), 136.4, 132.5 (**S4**), 132.4, 132.1 (**S4**), 129.1, 127.9, 127.8 (**S4**), 126.9 (**S4**), 126.6, 126.3, 126.2, 126.0 (**S4**), 124.9, 122.8, 115.0, 106.1 (**S4**), 105.8, 81.1, 62.6, 37.9, 37.1 (**S4**), 28.3. HRMS (ESI) calcd for $C_{23}H_{24}N_2O_3$ $(M + Na)^+$: m/z 399.16791, found 399.16950; calcd for $C_{23}H_{24}N_2O_3$ $(M+K)^+$: m/z 415.14185, found 415.14340.

*2-Methyl-7-(tetrahydrofuran-2-yl)isoquinolin-1(2H)-one (**43**).* Synthetized following general procedure B, the crude oil was chromatographed over SiO_2 (3:7 hexane/EtOAc) to afford

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43 as a yellow oil (23 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.65 (dd, J = 8.2, 1.9 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.04 (d, J = 7.3 Hz, 1H), 6.47 (d, J = 7.3 Hz, 1H), 5.02 (t, J = 7.2 Hz, 1H), 4.13 (dt, J = 8.3, 6.9 Hz, 1H), 3.96 (ddd, J = 8.3, 7.4, 6.4 Hz, 1H), 3.60 (s, 3H), 2.38 (m, 1H), 2.03 (m, 2H), 1.84 (ddt, J = 12.3, 8.6, 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 142.7, 136.4, 132.3, 129.9, 126.2, 126.1, 124.7, 106.0, 80.6, 69.0, 37.2, 34.9, 26.2. HRMS (ESI) calcd for $C_{14}H_{15}NO_2$ $(M + H)^+$: m/z 230.11756, found 230.11748; calcd for $C_{14}H_{15}NO_2$ $(M + Na)^+$: m/z 252.09950, found 252.09909.

*6-(1-Acryloylpyrrolidin-2-yl)-2-benzylisoquinolin-1(2H)-one (**31b**).* **31a** (35 mg, 0.086 mmol, 1 equiv) was treated by a 4 M solution of HCl.dioxane (0.7 mL, 2.84 mmol, 33 equiv) at room temperature for 2 h under argon. After complete evaporation of the solvent, the residue was taken up in dichloromethane (0.9 mL) and subsequently treated by triethylamine (27 μL, 0.19 mmol, 2.2 equiv) and acryloyl chloride (36 μL, 0.43 mmol, 5.0 equiv). The resulting mixture was stirred at room temperature for 18 h. The reaction was quenched upon the addition of an excess saturated NH_4Cl aqueous solution. The product was extracted with dichloromethane (×3). The organic phase was washed with distilled water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude oil was chromatographed over SiO_2 (1:9 hexane/EtOAc) to afford **31b** as a white solid (24 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.45 (m, 1H), 7.37−7.29 (m, 6H), 7.26 (m, 0.7H), 7.10 (m, 1H), 6.61 (m, 0.35H), 6.49−6.41 (m, 1H), 6.39 (m, 0.35H), 6.34 (m, 0.35H), 6.11 (m, 0.7H), 5.75 (m, 0.35H), 5.49 (m, 0.7H), 5.37 (m, 0.35H), 5.23 (s, 2H), 5.19 (m, 0.7H), 3.91 (m, 1H), 3.86−3.76 (m, 1H), 2.57−2.32 (m, 1H), 2.10−1.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 165.5, 164.7, 162.2, 162.0, 147.9, 147.8, 137.5, 137.3, 137.2, 136.9, 132.2, 131.6, 129.6, 129.2, 129.0, 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 125.7, 125.3, 124.7, 124.6, 122.7, 122.5, 106.7, 106.4, 61.3, 61.0, 51.9, 51.7, 47.9, 47.3, 36.2, 34.1, 24.2, 21.8. HRMS (ESI) calcd for $C_{23}H_{22}N_2O_2$ $(M + H)^+$ 359.1754, found 359.17524.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c04181.

^{1}H and ^{13}C NMR spectra for new compounds and supplementary reactions and control experiments (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Stephen Hanessian − *Department of Chemistry, Université de Montréal, Montréal, QC, Canada H3C 3J7*; orcid.org/0000-0003-3582-6972; Email: stephen.hanessian@umontreal.ca

Authors

Adrien Dumas − *Department of Chemistry, Université de Montréal, Montréal, QC, Canada H3C 3J7*

Jean-Baptiste Garsi − *Department of Chemistry, Université de Montréal, Montréal, QC, Canada H3C 3J7*

Guillaume Poissonnet − *CentEX Chemistry, Institut de Recherches Servier, 92150, France*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c04181

Notes

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■ REFERENCES

(1) Glushkov, V. A.; Shklyaev, Y. V. Synthesis of 1(2H)-Isoquinolones. (Review). *Chem. Heterocycl. Compd.* **2001**, *37*, 663−687.

(2) Chen, C.-Y.; Chang, F.-R.; Teng, C.-M.; Wu, Y.-C. Cheritamine, A New *N*-Fatty Acyl Tryptamine and Other Constituents from the Stems of *Annona cherimola*. *J. Chin. Chem. Soc.* **1999**, *46*, 77−86.

(3) Ahn, B. Z.; Zymalkowski, F. Siamin, ein Neues Isochinolon-Derivat aus Cassia Siamea. *Tetrahedron Lett.* **1976**, *17*, 821−824.

(4) Shamma, M.; Moniot, J. L. The Isoquinolones. In *Isoquinoline Alkaloids Research 1972−1977*; Plenum Press: New York/London, 1978; pp 57−60.

(5) Aly, Y.; Galal, A.; Wong, L. K.; Fu, E. W.; Lin, F.-T.; Duah, F. K.; Schiff, P. L., Jr. A Revision of the Structure of Isoquinolone Alkaloid Thalflavine. *Phytochemistry* **1989**, *28*, 1967−1971.

(6) Pettit, G. R.; Meng, Y.; Herald, D. L.; Graham, K. A. N.; Pettit, R. K.; Doubek, D. L. Isolation and Structure of Ruprechstyril from *Ruprechtia tangarana*. *J. Nat. Prod.* **2003**, *66*, 1065−1069.

(7) Okomoto, T.; Torii, Y.; Isogai, Y. Lycoricidinol and Lycoricidine, New Plant-growth Regulators in the Bulbs of *Lycoris radiata* Herb. *Chem. Pharm. Bull.* **1968**, *16*, 1860−1864.

(8) Gonzalez, D.; Martinot, T.; Hudlicky, T. A Short Chemoenzymatic Synthesis of (+)-Narciclasine. *Tetrahedron Lett.* **1999**, *40*, 3077−3080.

(9) Fisher, M. J.; Gunn, B.; Harms, C. S.; Kline, A. D.; Mullaney, J. T.; Nunes, A.; Scarborough, R. M.; Arfsten, A. E.; Skelton, M. A.; Um, S. L.; Utterback, B. G.; Jakubowski, J. A. Non-Peptide RGD Surrogates Which Mimic a Gly-Asp β-turn: Potent Antagonists of Platelet Glycoprotein IIb-IIIa. *J. Med. Chem.* **1997**, *40*, 2085−2101.

(10) Jagtap, P. G.; Baloglu, E.; Southan, G. J.; Mabley, J. G.; Li, H.; Zhou, J.; van Duzer, J.; Salzman, A. L.; Szabó, C. Discovery of Potent Poly(ADP-ribose) Polymerase-1 Inhibitors from the Modification of Indeno[1,2-*c*]isoquinolone. *J. Med. Chem.* **2005**, *48*, 5100−5103.

(11) Mood, A. D.; Premachandra, I. D. U. A.; Hiew, S.; Wang, F.; Scott, K. A.; Oldenhuis, N. J.; Liu, H.; Van Vranken, D. L. Potent Antifungal Synergy of Phtalazinone and Isoquinolones with Azoles Against *Candida* albicans. *ACS Med. Chem. Lett.* **2017**, *8*, 168−173.

(12) Kimura, M.; Waki, I.; Deguchi, Y.; Amemiya, K.; Maeda, T. 1(2*H*)-Isoquinolones as Potential Antiallergic Agents. *Chem. Pharm. Bull.* **1983**, *31*, 1277−1282.

(13) Trabanco, A. A.; Duvey, G.; Cid, J. M.; Macdonald, G. J.; Cluzeau, P.; Nhem, V.; Furnari, R.; Behaj, N.; Poulain, G.; Finn, T.; Lavreysen, H.; Poli, S.; Raux, A.; Thollon, Y.; Poirier, N.; D'Addona, D.; Andrés, J. I.; Lutjens, R.; Le Poul, E.; Imogai, H.; Rocher, J.-P. New positive allosteric modulators of the metabotropic glutamate receptor 2 (mGluR2): Identification and synthesis of *N*-propyl-8-chloro-6-substituted isoquinolones. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 971−976.

(14) Cheon, S. H.; Park, J. S.; Chung, B.-H.; Choi, B.-G.; Cho, W.-J.; Choi, S.-U.; Lee, C.-O. Synthesis and Structure-Activity Relationship Studies of Substituted Isoquinoline Analogs as Antitumor Agent. *Arch. Pharm. Res.* **1998**, *21*, 193−197.

(15) (a) de Meijere, A.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (b) Gladysz, J. A.

Introduction to Frontiers in Transition Metal Catalyzed Reactions (and a Brief Adieu). *Chem. Rev.* **2011**, *111*, 1167−1169.
(16) (a) Das, D.; Samanta, R. Iridium(III)-Catalyzed Regiocontrolled Direct Amidation of Isoquinolones and Pyridones. *Adv. Synth. Catal.* **2018**, *360*, 379−384. (b) Peng, P.; Wang, J.; Jiang, H.; Liu, H. Rhodium(III)-Catalyzed Site-Selective C-H Alkylation and Arylation of Pyridones Using Organoboron Reagents. *Org. Lett.* **2016**, *18*, 5376−5379. (c) Das, D.; Poddar, P.; Maity, S.; Samanta, R. Rhodium(III)-Catalyzed C6-Selective Arylation of 2-Pyridones and Related Heterocycles Using Quinone Diazides: Syntheses of Heteroarylated Phenols. *J. Org. Chem.* **2017**, *82*, 3612−3621. (d) Ni, J.; Zhao, H.; Zhang, A. Manganese(I)-Catalyzed C-H 3,3-Difluoroallylation of Pyridines and Indoles. *Org. Lett.* **2017**, *19*, 3159−3162. (e) Kumar, K. A.; Kannaboina, P.; Das, P. Ruthenium-catalyzed site-selective C-H arylation of 2-pyridones and 1-isoquinolinones. *Org. Biomol. Chem.* **2017**, *15*, 5457−5461. (f) Gao, F.; Han, X.; Li, C.; Liu, L.; Cong, Z.; Liu, H. Cobalt(III)-catalyzed site-selective C-H amidation of pyridines and isoquinolones. *RSC Adv.* **2018**, *8*, 32659−32663. (g) Xia, J.; Kong, L.; Zhou, X.; Zheng, G.; Li, X. Access to Substituted Propenoic Acids via Rh(III)-Catalyzed C-H Allylation of (Hetero)Arenes with Methyleneoxetanones. *Org. Lett.* **2017**, *19*, 5972−5975. (h) Tian, M.; Liu, B.; Sun, J.; Li, X. Rh(III)-Catalyzed C-C Coupling of Diverse Arenes and 4-Acyl-1-sulfonyltriazoles via C-H activation. *Org. Lett.* **2018**, *20*, 4946−4949. (i) Zhang, L.; Zheng, X.; Chen, J.; Cheng, K.; Jin, L.; Jiang, X.; Yu, C. Ru(II)-Catalyzed C6-selective C-H amidation of 2-pyridones. *Org. Chem. Front.* **2018**, *5*, 2969−2973. (j) Zhu, Y.-Q.; Niu, Y.-X.; Hui, L.-W.; He, J.-L.; Zhu, K. Reaction of Isoquinolin-1(2*H*)-Ones with Methylenecyclopropanes via Rhodium(III)-Catalyzed C-H Activation. *Adv. Synth. Catal.* **2019**, *361*, 2897−2903. (k) Fu, Y.; Wang, Z.; Zhang, Q.; Li, Z.; Liu, H.; Bi, X.; Wang, J. Ru(II)-catalyzed C6-selective C-H acylmethylation of pyridones using sulfoxonium ylides as carbene precursors. *RSC Adv.* **2020**, *10*, 6351−6355.
(17) (a) Kwon, S.; Kang, D.; Hong, S. Rh^{I}-Catalyzed Site-Selective Decarbonylative Alkenylation and Arylation of Quinolones under Chelation Assistance. *Eur. J. Org. Chem.* **2015**, *2015*, 3671−3678. (b) Kang, D.; Hong, S. Rh(III) and Ru(II)-Catalyzed Site-Selective C-H Alkynylation of Quinolones. *Org. Lett.* **2015**, *17*, 1938−1941.
(18) (a) Lee, S.; Mah, S.; Hong, S. Catalyst Controlled Divergent C4/C8 Site-Selective C-H Arylation of Isoquinolones. *Org. Lett.* **2015**, *17*, 3864−3867. (b) Shaikh, A. C.; Shinde, S. R.; Patil, N. T. Gold vs Rhodium Catalysis: Tuning Reactivity through Catalyst Control in the C-H Alkynylation of Isoquinolones. *Org. Lett.* **2016**, *18*, 1056−1059. (c) Zhu, Y.-Q.; He, J.-L.; Niu, Y.-X.; Kang, H.-Y.; Han, T.-F.; Li, H.-Y. $AgSbF_6$-Mediated Selective Thiolation and Selenylation at C-4 Position of Isoquinolin-1(2*H*)-ones. *J. Org. Chem.* **2018**, *83*, 9958−9967. (d) Sercel, A. D.; Sanchez, J. P.; Hollis Showalter, H. D. Simple Synthesis of 4-Substituted 1(2*H*)-Isoquinolinones via Electrophilic Trapping of Lithiated Mono- and Dianion Precursors. *Synth. Commun.* **2007**, *37*, 4199−4208. (e) Rimböck, K.-H.; Pöthig, A.; Bach, T. Photocycloaddition and Rearrangement Reactions in a Putative Route to the Skeleton of Plicamine-Type Alkaloids. *Synthesis* **2015**, *47*, 2869−2884. (f) Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. Discovery of Isoquinolone Indole Acetic Acids as Antagonists of Chemoattractant Receptor Homologous Molecule Expressed on Th2 Cells (CRTH2) for the Treatment of Allergic Inflammatory Diseases. *J. Med. Chem.* **2014**, *57*, 1299−1322. (g) Fish, P. V.; Barber, C. G.; Brown, D. G.; Butt, R.; Collis, M. G.; Dickinson, R. P.; Henry, B. T.; Horne, V. A.; Huggins, J. P.; King, E.; O'Gara, M.; McCleverty, D.; McIntosh, F.; Philipps, C.; Webster, R. Selective Urokinase-Type Plasminogen Activator Inhibitors. 4.1-(7-Sulfonamidoisoquinolinyl)guanidines. *J. Med. Chem.* **2007**, *50*, 2341−2351. (h) Price, D. A.; James, K.; Osborne, S.; Harbottle, G. W. Selective fluorination of 1-hydroxyisoquinolines using SelectFluor. *Tetrahedron Lett.* **2007**, *48*, 7371−7373.
(19) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. Rhodium(III)- and Ruthenium(II)-Catalyzed Olefination of Isoquinolones. *Org. Lett.* **2012**, *14*, 4166−4169.
(20) For recent procedures see: (a) Bennett, M. J.; Wu, Y.; Boloor, A.; Matuszkiewicz, J.; O'Connell, S. M.; Shi, L.; Stansfield, R. K.; Del Rosario, J. R.; Veal, J. M.; Hosfield, D. J.; Xu, J.; Kaldor, S. W.; Stafford, J. A.; Betancort, J. M. Design, synthesis and biological evaluation of novel 4-phenylisoquinolinone BET bromodomain inhibitors. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 1811−1816. (b) Xu, M.-Y.; Wang, C.; Jiang, W.-T.; Xiao, B. Synthesis and Application of Heterocyclic Germatranes via Rhodium-Catalyzed Directed C-H Activation/Annulation with Alkynyl Germatranes and Palladium-Catalyzed Cross-Coupling. *Adv. Synth. Catal.* **2020**, *362*, 1706−1711.
(21) Ray, P.; Wright, J.; Adam, J.; Boucharens, S.; Black, D.; Brown, A. R.; Epemolu, O.; Fletcher, D.; Huggett, M.; Jones, P.; Laats, S.; Lyons, A.; de Man, J.; Morphy, R.; Sherborne, B.; Sherry, L.; van Straten, N.; Westwood, P.; York, M. Optimisation of 6-substituted isoquinolin-1-amine based ROCK-I inhibitors. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1084−1088.
(22) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. The impact of aromatic ring count on compound developability: further insights by examining carbo- and hetero-aromatic and −aliphatic ring types. *Drug Discovery Today* **2011**, *16*, 164−171.
(23) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756. (b) Lovering, F. Escape from Flatland 2: complexity and promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515−519.
(24) Li, L.; Feng, J.; Liu, Y.; Ren, P.; Liu, Y. Fused *N*-Heterocyclic Compounds and Methods of Use Thereof. WO2018140598A1, 2018.
(25) Lanman, B. A.; Allen, J. K.; Allen, J. G.; Amegadzie, A. K.; Ashton, K. S.; Booker, S. K.; Chen, J. J.; Chen, N.; Frohn, M. J.; Goodman, G.; Kopecky, D. J.; Liu, L.; Lopez, P.; Low, J. D.; Ma, V.; Minatti, A. E.; Nguyen, T. T.; Nishimura, N.; Pickrell, A. J.; Reed, A. B.; Shin, Y.; Siegmund, A. C.; Tamayo, N. A.; Tegley, C. M.; Walton, M. C.; Wang, H.-L.; Wurz, R. P.; Xue, M.; Yang, K. C.; Achanta, P.; Bartberger, M. D.; Canon, J.; Hollis, L. S.; McCarter, J. D.; Mohr, C.; Rex, K.; Saiki, A. Y.; San Miguel, T.; Volak, L. P.; Wang, K. H.; Whittington, D. A.; Zech, S. G.; Lipford, J. R.; Cee, V. J. Discovery of a Covalent Inhibitor of $KRAS^{G12C}$ (AMG 510) for the Treatment of Solid Tumors. *J. Med. Chem.* **2020**, *63*, 52−65.
(26) (a) Everson, D. A.; Shrestha, R.; Weix, D. J. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 920−921. (b) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146−6159. (c) Everson, D. A.; Buonomo, J. A.; Weix, D. J. Nickel-Catalyzed Cross-Electrophile Coupling of 2-Chloropyridines with Alkyl Bromides. *Synlett* **2014**, *25*, 233−238.
(27) (a) Wang, S.; Qian, Q.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Halides with Secondary Alkyl Bromides and Allylic Acetate. *Org. Lett.* **2012**, *14*, 3352−3355. (b) Wang, J.; Zhao, J.; Gong, H. Nickel-catalyzed methylation of aryl halides/tosylates with methyl tosylate. *Chem. Commun.* **2017**, *53*, 10180−10183. (c) Wang, X.; Wang, S.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Bromides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 11562−11565.
(28) (a) Molander, G. A.; Traister, K. M.; O'Neill, B. T. Reductive Cross-Coupling of Nonaromatic, Heterocyclic Bromides with Aryl and Heteroaryl Bromides. *J. Org. Chem.* **2014**, *79*, 5771−5780. (b) Molander, G. A.; Traister, K. M.; O'Neill, B. T. Engaging Nonaromatic, Heterocyclic Tosylates in Reductive Cross-Coupling with Aryl and Heteroaryl Bromides. *J. Org. Chem.* **2015**, *80*, 2907−2911.
(29) For selected reviews on alkyl sp^3/aryl sp^2 Ni-catalyzed reductive cross coupling reactions, see: (a) Richmond, E.; Moran, J. Recent Advances in Nickel Catalysis Enabled by Stoichiometric Metallic Reducing Agents. *Synlett* **2018**, *50*, 499−513. (b) Weix, D. J. Methods

https://dx.doi.org/10.1021/acsomega.0c04181
ACS Omega 2020, 5, 27591−27606

and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767−1775. (c) Gu, J.; Wang, X.; Xue, W.; Gong, H. Nickel-catalyzed reductive coupling of alkyl halides with other electrophiles: concept and mechanistic considerations. *Org. Chem. Front.* **2015**, *2*, 1411−1421. (d) Wang, X.; Dai, Y.; Gong, H. Nickel-Catalyzed Reductive Couplings. *Top. Curr. Chem.* **2016**, *374*, No. 43. (e) Goldfogel, M. J.; Huang, L.; Weix, D. J. Cross-Electrophile Coupling: Principles and New reactions. In *Nickel Catalysis in Organic Synthesis: Methods and reactions*; Ogoshi, S., Ed.; Wiley-VCH: Weinheim, 2019; pp 183−222.

(30) For a recent review see: Twilton, J.; Le, C. C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The merger of transition metal and photocatalysis. *Nat. Rev. Chem.* **2017**, *1*, No. 0052.

(31) For reviews on related photocatalytic reactions, see: (a) Tucker, J. W.; Stephenson, C. R. J. Shining Light on Photoredox Catalysis: Theory and Synthetic Applications. *J. Org. Chem.* **2012**, *77*, 1617−1622. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363. (c) Xie, J.; Jin, H.; Xu, P.; Zhu, C. When C-H bond functionalization meets visible-light photoredox catalysis. *Tetrahedron Lett.* **2014**, *55*, 36−48. (d) Schultz, D. M.; Yoon, T. P. Solar Synthesis: Prospects in Visible Light Photocatalysis. *Science* **2014**, *343*, No. 1239176. (e) Courant, T.; Masson, G. Recent Progress in Visible-Light Photoredox-Catalyzed Intermolecular 1,2-Difunctionalization of Double Bonds via an ATRA-Type Mechanism. *J. Org. Chem.* **2016**, *81*, 6945−6952. (f) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **2016**, *116*, 10035−10074. (g) Silvi, M.; Melchiorre, P. Enhancing the potential of enantioselective organocatalysis with light. *Nature* **2018**, *554*, 41−49. (h) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy transfer catalysis mediated by visible light: principles, applications, directions. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202. (i) Zou, Y.-Q.; Hörmann, F. M.; Bach, T. Iminium and enamine catalysis in enantioselective photochemical reactions. *Chem. Soc. Rev.* **2018**, *47*, 278−290. (j) Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. Mechanistic Studies in Photocatalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 3730−3747. (k) Petzold, D.; Giedyk, M.; Chatterjee, A.; König, B. A Retrosynthetic Approach for Photocatalysis. *Eur. J. Org. Chem.* **2019**, *20*, 1193−1244. (l) Stephenson, C. R. J.; Yoon, T. P.; MacMillan, D. W. C. *Visible Light Photocatalysis in Organic Chemistry*; Wiley-VCH: Weinheim, 2018.

(32) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215−5246.

(33) Biswas, S.; Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 16192−16197.

(34) Hanessian, S.; Kagotani, M.; Komaglou, K. Design and Reactivity of Organic Functional Groups − 2-pyridylsulfonates as Nucleofugal Esters: Remarkably Mild Transformations into Halides and Olefins. *Heterocycles* **1989**, *28*, 1115−1120.

(35) (a) Ren, Q.; Jiang, F.; Gong, H. DFT study of the single electron transfer mechanisms in Ni-Catalyzed reductive cross-coupling of aryl bromide and alkyl bromide. *J. Organomet. Chem.* **2014**, *770*, 130−135. (b) Lin, Q.; Diao, T. Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 17937−17948. (c) Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H. Ni-Catalyzed Reductive Coupling of Electron-Rich Aryl Iodides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2018**, *140*, 14490−14497. (d) Diccianni, J. B.; Diao, T. Mechanisms of Nickel-Catalyzed Cross-Coupling Reactions. *Trends Chem.* **2019**, *1*, 830−844.

(36) Prinsell, M. R.; Everson, D. A.; Weix, D. J. Nickel-catalyzed, sodium iodide-promoted reductive dimerization of alkyl halides, alkyl pseudohalides, and allylic acetates. *Chem. Commun.* **2010**, *46*, 5743−5745.

(37) (a) Cassar, L.; Foà, M. Nickel-Catalyzed Carbonylation of Aromatic Halides at Atmospheric Pressure of Carbon Monoxide. *J. Organomet. Chem.* **1973**, *51*, 381−393. (b) Colon, I.; Kelsey, D. Coupling of Aryl Chlorides by Nickel and Reducing Metals. *J. Org. Chem.* **1986**, *51*, 2627−2637. (c) Zembayashi, M.; Tamao, K.; Yoshida, J.-I.; Kumada, M. Nickel-Phosphine Complex-Catalyzed Homo Coupling of Aryl Halides in the Presence of Zinc Powder. *Tetrahedron Lett.* **1977**, *18*, 4089−4092.

(38) Klein, A.; Kaiser, A.; Wielandt, W.; Belaj, F.; Wendel, E.; Bertagnolli, H.; Záliš, S. Halide Ligands-More Than Just σ-Donors? A Structural and Spectroscopic Study of Homologous Organonickel Complexes. *Inorg. Chem.* **2008**, *47*, 11324−11333.

(39) Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. Nickel-catalyzed cross-coupling of unactivated alkyl halides using bis-(pinacolato)diboron as reductant. *Chem. Sci.* **2013**, *4*, 4022−4029.

(40) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. Enantioselective Decarboxylative Arylation of α-Amino Acids via the Merger of Photoredox and Nickel Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 1832−1835.

(41) Liang, Z.; Xue, W.; Lin, K.; Gong, H. Nickel-Catalyzed Reductive Methylation of Alkyl Halides and Acid Chlorides with Methyl *p*-Tosylate. *Org. Lett.* **2014**, *16*, 5620−5623.

(42) For early studies see: (a) Bakac, A.; Espenson, J. H. Mechanistic Investigation of Carbon-Carbon Bond Formation in the Reduction of Alkyl Halides by Organonickel Complexes in Aqueous Solution. *J. Am. Chem. Soc.* **1986**, *108*, 719−723. See also: (b) Anderson, T. J.; Jones, G. D.; Vicic, D. A. Evidence for a Ni^I Active Species in the Catalytic Cross-Coupling of Alkyl Electrophiles. *J. Am. Chem. Soc.* **2004**, *126*, 8100−8101.

(43) (a) Komeyama, K.; Ohata, R.; Kiguchi, S.; Osaka, I. Highly nucleophilic vitamin B_{12}-assisted nickel-catalysed reductive coupling or aryl halides and non-activated alkyl tosylates. *Chem. Commun.* **2017**, *53*, 6401−6404. (b) Ganson, J. R.; Schulenberg, S.; Closson, W. D. Competitive C-O and S-O cleavage mechanisms in reaction of alkyl alkanesulfonates with arene anion radicals. *Tetrahedron Lett.* **1970**, *11*, 4397−4400. (c) Lipshutz, B. H.; Wilhelm, R. S.; Nugent, S. T.; Daniel Little, L.; Baizer, M. M. Electrochemical Peak Potentials of Typical Substrates Used for Coupling Reactions with Organo-cuprates: Effects of Solvent. *J. Org. Chem.* **1983**, *48*, 3306−3308. (d) Ashby, E. C.; Argyropoulos, J. N. Single Electron Transfer in the Reaction of Enolates with Alkyl Halides. *J. Org. Chem.* **1985**, *50*, 3274−3283. (e) Komeyama, K.; Michiyuki, T.; Osaka, I. Nickel/Cobalt-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling of Alkyl Halides with Alkyl Tosylates. *ACS Catal.* **2019**, *9*, 9285−9291.

(44) (a) Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. Cobalt co-catalysis for cross-electrophile coupling: diarylmethanes from benzyl mesylates and aryl halides. *Chem. Sci.* **2015**, *6*, 1115−1119. (b) Komeyama, K.; Yamahata, Y.; Osaka, I. Nickel and Nucleophilic Cobalt-Catalyzed Trideuteriomethylation of Aryl Halides Using Trideuteriomethyl *p*-Toluenesulfonate. *Org. Lett.* **2018**, *20*, 4375−4378. (c) Komeyama, K.; Tsunemitsu, R.; Michiyuki, T.; Yoshida, H.; Osaka, I. Ni/Co-Catalyzed Homo-Coupling of Alkyl Tosylates. *Molecules* **2019**, *24*, 1458. (d) Duan, J.; Du, Y.-F.; Pang, X.; Shu, X.-Z. Ni-catalyzed cross-electrophile coupling between vinyl/aryl and alkyl sulfonates: synthesis of cycloalkenes and modification of peptides. *Chem. Sci.* **2019**, *10*, 8706−8712. (e) Michiyuki, T.; Osaka, I.; Komeyama, K. Reductive amidation of alkyl tosylates with isocyanates by a Ni/Co-dual catalytic system. *Chem. Commun.* **2020**, *56*, 1247−1250. (f) Sanford, A. B.; Thane, T. A.; McGinnis, T. M.; Chen, P.-P.; Hong, X.; Jarvo, E. R. Nickel-Catalyzed Alkyl-Alkyl Cross-Electrophile Coupling Reaction of 1,3-Dimesylates for the Synthesis of Alkylcyclopropanes. *J. Am. Chem. Soc.* **2020**, *142*, 5017−5023.

(45) For the reaction of iodides and tosylates with Grignard reagents to form sp^3/sp^2 bonds, see for example: (a) Gonnard, L.; Guérinot, A.; Cossy, J. Cobalt-Catalyzed Cross-Coupling of 3- and 4-Iodopiperidines with Grignard Reagents. *Chem. − Eur. J.* **2015**, *21*, 12797−12803. and references therein. See also (b) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. Copper-Catalyzed Cross-Coupling of Nonactivated Secondary Alkyl Halides and Tosylates with Secondary Alkyl Grignard Reagents. *J. Am.*

https://dx.doi.org/10.1021/acsomega.0c04181
ACS Omega 2020, 5, 27591−27606

Chem. Soc. **2012**, *134*, 11124−11127. (c) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. Nickel-Catalyzed Cross-Coupling Reaction of Grignard Reagents with Alkyl Halides and Tosylates: Remarkable Effect of 1,3-Butadienes. *J. Am. Chem. Soc.* **2002**, *124*, 4222−4223.

(46) Newcomb, M. Kinetics of Radical Reactions: Radical Clocks. In *Radicals in Organic Synthesis*, 1st ed.;Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. *1*, pp 316−336.

(47) Savin, K. A. Radicals and Radical Anions. In *Writing Reaction Mechanisms in Organic Chemistry*, 3rd ed.; Savin, K. A., Ed.; Academic Press, 2015; pp 237−292.

(48) Heinz, C.; Lutz, J. P.; Simmons, E. M.; Miller, M. M.; Ewing, W. R.; Doyle, A. G. Ni-Catalyzed Carbon-Carbon Bond-Forming Reductive Amination. *J. Am. Chem. Soc.* **2018**, *140*, 2292−2300.

(49) (a) Cherney, A. H.; Reisman, S. E. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Vinyl and Benzyl Electrophiles. *J. Am. Chem. Soc.* **2014**, *136*, 14365−14368. In other work, rearrangement products can be seen. See for example (b) Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling To Access 1,1-Diarylalkanes. *J. Am. Chem. Soc.* **2017**, *139*, 5684−5687. (c) Kadunce, N. T.; Reisman, S. E. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling between Heteroaryl Iodides and α-Chloronitriles. *J. Am. Chem. Soc.* **2015**, *137*, 10480−10483.

(50) (a) Zuo, Z.; MacMillan, D. W. C. Decarboxylative Arylation of α-Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014**, *136*, 5257−5260. (b) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. Merging photoredox with nickel catalysis: Coupling of α-carboxyl sp^3-carbons with aryl halides. *Science* **2014**, *345*, 437−440. (c) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. Merging Photoredox and Nickel Catalysis: Decarboxylative Cross-Coupling of Carboxylic Acids with Vinyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 624−627. (d) Chu, L.; Lipshultz, M.; MacMillan, D. W. C. Merging Photoredox and Nickel Catalysis: The Direct Synthesis of Ketones by the Decarboxylative Arylation of α-Oxo Acids. *Angew. Chem., Int. Ed.* **2015**, *54*, 7929−7933.

(51) For alternative strategies, see: (a) Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J. T.; Cornella, J.; Vokits, B.; Shaw, S. A.; Baran, P. S. Nickel-Catalyzed Cross-Coupling of Redox-Active Esters with Boronic Acids. *Angew. Chem., Int. Ed.* **2016**, *55*, 9676−9679. (b) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. Practical Ni-Catalyzed Aryl-Alkyl Cross-Coupling of Secondary Redox-Active Esters. *J. Am. Chem. Soc.* **2016**, *138*, 2174−2177. (c) Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S. Redox-Active Esters in Fe-Catalyzed C-C Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 11132. For reviews see: (d) Sandfort, F.; O'Neill, M. J.; Cornella, J.; Wimmer, L.; Baran, P. S. Alkyl-(Hetero)Aryl Bond Formation via Decarboxylative Cross-Coupling: A Systematic Analysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 3319−3323. (e) Rodríguez, N.; Goossen, L. J. Decarboxylative coupling reactions: a modern strategy for C-C-bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5030−5048. (f) Moon, P. J.; Lundgren, R. J. Metal-Catalyzed Ionic Decarboxylative Cross-Coupling Reactions of $C(sp^3)$ Acids: Reaction Development, Mechanisms, and Application. *ACS Catal.* **2020**, *10*, 1742−1753. (g) Arshadi, S.; Ebrahimiasl, S.; Hosseinian, A.; Monfared, A.; Vessally, E. Recent developments in decarboxylative cross-coupling reactions between carboxylic acids and N-H compounds. *RSC Adv.* **2019**, *9*, 8964−8976.

(52) See for example (a) Bauer, R. A. Covalent inhibitors in drug discovey: from accidental discoveries to avoided liabilities and designed therapies. *Drug DiscoveryToday* **2015**, *20*, 1061−1073. (b) Baillie, T. A. Targeted Covalent Inhibitors for Drug Design. *Angew. Chem., Int. Ed.* **2016**, *55*, 13408−13421. (c) Singh, J.; Petter, R. C.; Baillie, T. A.; Whitty, A. The resurgence of covalent drugs. *Nat. Rev. Drug Discovery* **2011**, *10*, 307−317. (d) Strelow, J. M. A Perspective on the Kinetics of Covalent and Irreversible Inhibition. *SLAS Discovery* **2017**, *22*, 3−20.

https://dx.doi.org/10.1021/acsomega.0c04181
ACS Omega 2020, 5, 27591−27606