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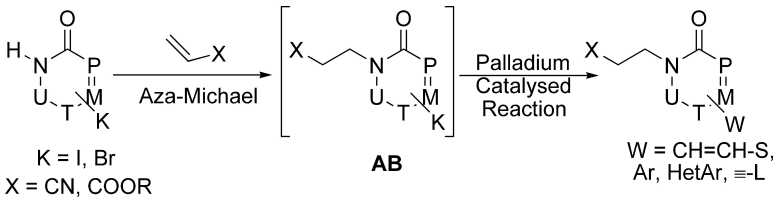

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Straightforward Entry to Libraries of Diversely Substituted Azinones by a Consecutive Aza-Michael/Palladium-Catalyzed Functionalization Strategy

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A highly divergent, flexible, and conceptually simple sequence allowing the parallel solution-phase assembly of functionalized azinone libraries has been developed in a one-pot consecutive fashion. Structural decoration of in situ-generated heterocyclic aza-Michael adducts **AB** was accomplished by exploiting the diversity potential of Heck, Suzuki, Sonogashira, and Stille reactions.

In the past two decades, all parts of the drug discovery process have undergone radical changes.[1] In response to the need to discover valuable, pharmacologically useful compounds and to shorten the time required for preclinical research, medicinal chemists have incorporated successful new concepts and methodologies into the laborious process of lead discovery and lead optimization. Selectivity, atom economy, time saving, environmental friendliness, cost-effectiveness, diversity, and druglike properties, as well as the reconciliation of molecular complexity with experimental simplicity, are some of the key pieces of the puzzle that must be assembled by modern medicinal chemists to achieve the maximum efficiency during library synthesis. Most of these characteristics are met by multicomponent,[2] domino,[3] and consecutive[4] reactions, which have emerged as powerful strategies in combinatorial chemistry,[5] allowing generation of diverse and complex molecules by the formation of new covalent bonds in one-pot transformation. One of the most promising strategies in this field is the use of transition-metal-catalyzed reactions,[6] which provide powerful tools for creating molecular diversity matching the space of biological targets with relevant chemistry. However, despite their enormous potential, examples of such transformations in library production are still rare,[7] and there is, therefore, a dearth of new methodologies that are able to deliver large heterocyclic-based libraries. With the exception of the above-cited newer strategies and some elegant examples,[8] one-pot synthesis of heterocyclic libraries[9] is still generally dominated by the use of classical heteroannulation approaches,[10] which provide collections of moderate functional diversity and limited scaffold variability.

Despite the widely documented pharmacological activities of azinones[11] and the limited number of combinatorial procedures available for accessing libraries of these privileged scaffolds, we recently embarked on a program[12,13] to implement flexible, conceptually simple, and synthetically promising approaches for achieving rapid access to structurally exclusive libraries with improved skeletal and functional diversity. Herein, we document the synthesis of libraries of functionalized azinones, in a one-pot fashion, by decoration of the in situ-generated heterocyclic Michael adducts **AB** using Heck, Suzuki, Sonogashira, or Stille reactions as the source of diversity (Figure 1). The libraries are not only novel but also exemplify the first consecutive aza-Michael/palladium-catalyzed sequence in a heterocyclic system exploited in a combinatorial manner and will contribute to expanding the molecular diversity of azinone libraries.

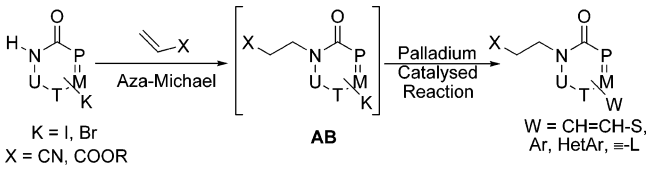

Figure 1. Consecutive aza-Michael/palladium-catalyzed approach for preparing libraries of skeletal and functional diverse azinones.

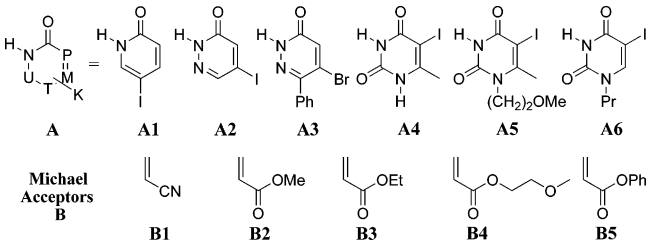

Figure 2. Scaffolds and Michael acceptors represented by structures **A** and **B**.

Investigation of the feasibility of this one-pot sequence relied on the results of a previous study of the Heck alkenylation of 5-halopyridazin-3(2*H*)-ones,[14] which clearly demonstrated that conjugate addition of the heterocyclic NH group to the negatively substituted olefin is favored over the desired cross-coupling reaction. Thus, 2,5-disubstituted pyridazin-3(2*H*)-ones were isolated in moderated yields when an excess of the corresponding acrylate was used,[14] a finding attributed to a consecutive aza-Michael/Heck coupling

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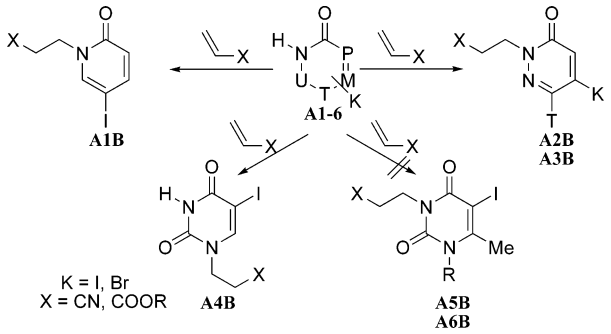
Scheme 1. Conjugate Addition of Scaffolds **A** on the Michael Acceptors **B**[20]



sequence. Inspired by these findings and recognizing the potential of such methodologies in library synthesis, we were further intrigued about the scope of such transformations when extended to other palladium-catalyzed reactions and azinones.

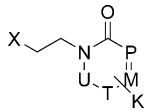
The conjugate addition of nitrogenated nucleophiles to α,β-unsaturated compounds is a powerful but underrepresented procedure among the available synthetic methods of C−N bond formation. Although the products of aza-Michael addition (e.g., β-amino carbonyl compounds) are ubiquitous motifs in natural products,[15] a survey of the relevant literature[16] revealed that effective catalysts for this transformation have only recently been reported. Moreover, the successful use of *N*-nucleophiles without special activation (e.g., aromatic amines or carbamates) remains an unsolved problem of great interest in organic synthesis. To our surprise, very few studies describing such conjugate addition to azinones have been reported.[17] The present study, therefore, began with the selection of a chemset of highly activated, sterically unhindered Michael acceptors **B** (Figure 1), which was submitted to reaction with our in-house array of azinones **A**[18] (Figure 1). These scaffolds (**A**) contain high skeletal diversity and two [or three (**A4**)] orthogonal sites for diversification; namely, the NH group and the halogen (I or Br).

The absence of comprehensive studies on this subject, as well as the predicted differences in reactivity within **A** (Figure 1), required carrying out an exhaustive examination of the scope of the base-catalyzed conjugate addition to α,β-unsaturated carbonyl compounds. Taking into account that some palladium-catalyzed reactions require particular experimental conditions, the main goal of this preliminary study was to identify a set of optimal, mild, and selective conditions for each scaffold, which would then facilitate the implementation of consecutive transformations. Exploiting the advantages offered by combinatorial chemistry in process optimization,[19] the effects of different bases (TEA, DIPEA, DBU, K_2CO_3, and KOH), solvents (DMF, THF, MeCN, toluene, DME, DME/H_2O, etc.), and temperatures (25, 40, 50, and 80 °C) were screened for the reaction of **A** with a subset of Michael acceptors **B** (Scheme 1, Table 1).

The results of these experiments showed that, unlike in the case of 1-substituted pyrimidine-2,4-(3*H*)-diones (**A5** and **A6**), the reaction led to almost quantitative formation (Table 1) of the desired adducts **AB** (Scheme 1) by using stoichiometric quantities of the starting materials. The high efficiency and regioselectivity found for the 5-iodoracil **A4** (Table 1) is consistent with reported data.[21] It is also particularly noteworthy that during the study of the conjugate addition on **A4**, we were not able to isolate products of double addition, even when using a small excess of acrylate (**B**). Such reactivity could be used to explain the observed failures when submitting the structurally related derivatives **A5** and **A6** to a similar reaction. Unfortunately, the use of other conditions (e.g., tetrabutylammonium hydroxide in pyridine)[22] or catalysts[16] ($LiClO_4$ or $CeCl_3$−NaI) did not significantly increase the yields of the conjugate addition on 1-substituted uracils (**A5** and **A6**), and therefore, these compounds were not considered for the development of consecutive transformations.

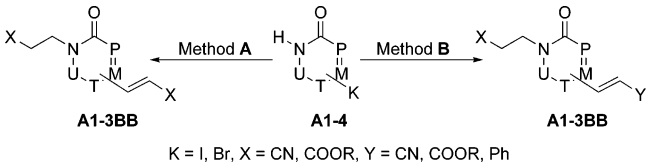
The conjugate addition of **A** on the Michael acceptors **B** is only partially dependent on the solvent, with the solubility

Table 1. Structure of Representative Michael Adducts (AB) Obtained[20]



entry	compd	X	conditions	yield (%)
1	**A1B2**	COOMe	TEA, DMF, 80 °C	89
			K_2CO_3, DMF, 80 °C	95
2	**A1B5**	COO−$(CH_2)_2$OMe	TEA, DMF, 80 °C	92
			K_2CO_3, DME/H_2O, 70 °C	90
3	**A2B1**	CN	TEA, DMF, 80 °C	88
			K_2CO_3, DMF, 80 °C	95
4	**A2B3**	COOMe	TEA, MeCN, 80 °C	89
			K_2CO_3, MeCN, 80 °C	98
5	**A3B1**	CN	TEA, DMF, 80 °C	90
			K_2CO_3, DME/H_2O, 80 °C	97
6	**A3B2**	COOMe	K_2CO_3, DMF, 80 °C	97
			K_2CO_3, DME/H_2O, 80 °C	93
7	**A4B2**	COOMe	K_2CO_3, MeCN/H_2O, 40 °C	93
			K_2CO_3, DME/H_2O, 70 °C	95
8	**A4B3**	COOEt	K_2CO_3, MeCN/H_2O, 40 °C	94
			K_2CO_3, DME/H_2O, 40 °C	89
9	**A4B3**	COOEt	TEA, MeCN, 40 °C	0
			TEA, DMF, 40 °C	0

Scheme 2. Synthesis of Azinone Libraries Using the Aza-Michael/Heck Sequence[a]



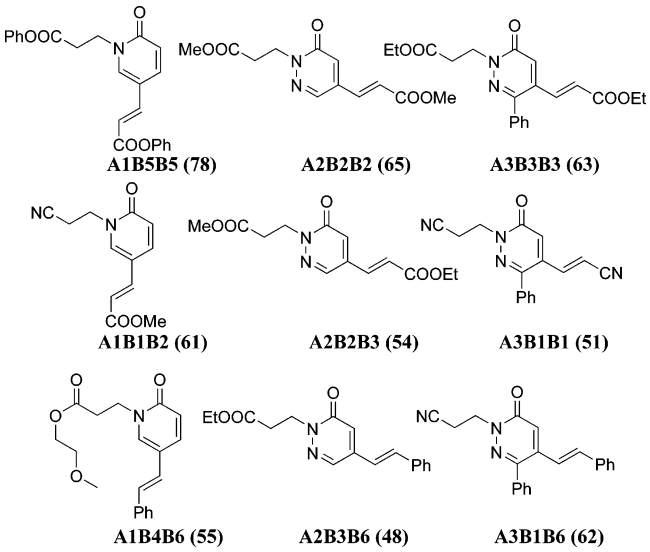
[a] Method A: CH_2═CH−X (3 equiv), base (2.5 equiv, K_2CO_3 for **A1** and **A2** or TEA for **A3**), catalyst (10% Pd/C for **A1** and **A2**, $Cl_2Pd[P(o\text{-Tolyl})_3]_2$ (5 mol %) for **A3**), solvent (MeCN or DMF). Method B: (1) CH_2═CH−X (1 equiv), base (2.5 equiv, K_2CO_3 for **A1** and **A2** or TEA for **A3**), solvent (MeCN or DMF); (2) CH_2═CH−Y (3 equiv), catalyst (10% Pd/C for **A1** and **A2**, $Cl_2Pd[P(o\text{-Tolyl})_3]_2$ (5 mol %) for **A3**).

of the starting azinone being the most important limitation. Taking into account our overall aim, transformations were optimized in three different solvents that are usually used in cross-coupling reactions [DMF, CH_3CN, or DME/H_2O (3:1)]. Although basic catalysis is required, as shown in Table 1, the reaction proved to be tolerant to most of the bases tested, providing generally similar results, independently of its nature (e.g. TEA or K_2CO_3). For some azinones (**A2**, **A3**), the reaction proceeded rapidly, even at room temperature, completely consuming the Michael acceptor within 2−4 h. Despite the expected similar reactivity of the heterocyclic lactame (CONH) group of the azinones **A** and the carbamate group (which has been recognized as a poor substrate in aza-Michael reactions requiring catalysts) we found that the former transformations did not require special activation or the presence of any metallic catalyst. Confirmation of such a result greatly simplified the identification of optimal conditions because the presence of these metallic ions could interfere with the subsequent cross-coupling reaction.

The observed degree of efficiency (Table 1) fulfilled our expectations, and we therefore began a study to investigate the development of new consecutive transformations involving cross-coupling reactions on the halogen atom of the in situ-generated adducts **AB**. In light of recent observations[23−25] on the use of palladium on charcoal as a successful catalyst in different palladium-assisted reactions, the use of this cheap and easy-to-remove agent was evaluated as an alternative catalyst to the homogeneous palladium catalysts usually employed for each transformation.

For obvious reasons, initial studies were focused on the aza-Michael/Heck sequence (Scheme 2), and the above optimized conditions were used. Scaffolds **A1**−**4** were reacted with an excess (3 equiv) of the corresponding Michael acceptor (**B**) under the experimental conditions depicted in Scheme 2. Transformations reached complete conversion in 2−8 h, and appropriate workup and chromatographic purification provided the target azinones (Chart 1). As observed, conditions were quite general; the optimal conditions were a combination of Pd/C and K_2CO_3 as catalyst and base, respectively. The only exception was scaffold **A3** (which contains a bromine atom as reactive halide), which required the use of $Cl_2Pd[P(o\text{-Tolyl})_3]_2$ and TEA. The results clearly demonstrated the effectiveness of the proposed method (Chart 1, compounds **A1B5B5**, **A2B2B2**, and **A3B3B3**), and the yields varied considerably, depending on the heterocyclic core (**A**), and ranged from good to satisfactory in the case of pyridin-2(1*H*)-one (**A1**) and pyridazin-3(2*H*)-ones (**A2**, **A3**) to poor (<20%) in the case of uracil (**A4**). One remarkable feature of this simple one-pot sequence is its divergence and its consequent potential contribution to diversity. As observed in Chart 1, the Michael acceptor partner (**B**) can be differentially incorporated at the reactive sites in the heterocyclic backbone, generating two distinct functional diversities, depending on the reaction that allows it to attach to the scaffold (Scheme 2, Chart 1).

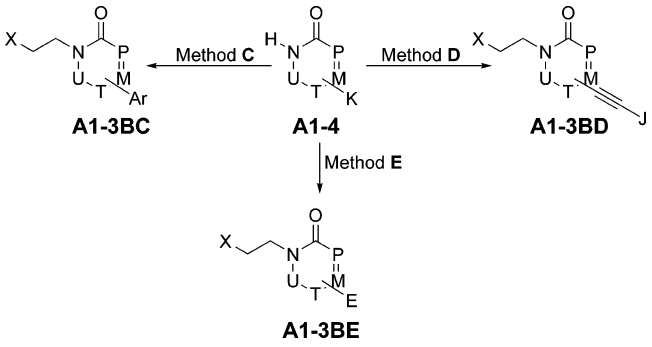
Chart 1. Representative Azinones Obtained by the Aza-Michael/Heck Sequence[20]



Having confirmed the feasibility of the simplest-case proposed approach and to extend the scope and generality of the protocol, the simultaneous introduction of diversity by sequential reaction of **A1**−**4** with two different olefins was considered (Scheme 2). During these experiments, variable quantities (3−4 equiv) of the second olefin (CH_2═CH−Y) were added to a preincubated equimolecular (2−4 h) mixture of **A**, the acrylic acid derivative (CH_2═CH−X) and base (TEA or K_2CO_3) in DMF or MeCN, and then the appropriate catalysts (10% Pd/C or $Cl_2Pd[P(o\text{-Tolyl})_3]_2$) were added. We were delighted to find that regioselectivity can be easily controlled by addition of a moderate excess (3 equiv) of the olefin, retaining the alkenyl functionality in the heterocyclic core. Although reported yields have been not completely optimized,[20] satisfactory yields of the desired azinones were obtained. As can be seen (Chart 1), diverse substituents (X/Y) present in the starting olefins were (**B**) well tolerated, not only for the aza-Michael but also during the Heck coupling. As exemplified for Michael acceptors (**B1**−**B5**) and for styrene (**B6**), this operationally simple one-pot procedure maintains the general scope of the Heck reaction, allowing the introduction into the scaffold of diverse alkenyl fragments either containing or not containing electron-withdrawing groups (e.g., **A1B4B6**, **A2B3B6**, **A3B1B6**).

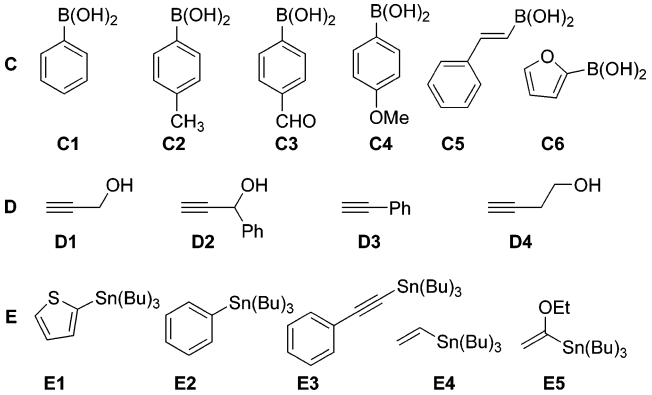
As observed in Chart 1, the sequence appeared ideally suited for the solution-phase production of pyridin-2(1*H*)-one (**A1**) and pyridazin-3(2*H*)-one (**A2**, **A3**) libraries; but was not applicable to the pyrimidin-2,4(1*H*,3*H*)-dione (**A4**), which afforded a mixture of significant amounts of the Michael adducts (**A4B**) and uncharacterized highly polar side products. With the aim of establishing the optimal conditions for this system, some adducts **A4B** were prepared, isolated,

Scheme 3. One-Pot Consecutive Aza-Michael/Palladium-Catalyzed Functionalization of Azinones **A**[a]



[a] Method C: (1) CH_2═CH-X (1.1 equiv), K_2CO_3 (2.5 equiv), DME/H_2O, 80 °C; (2) Ar−$B(OH)_2$ (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), 90 °C. Method D: (1) CH_2═CH−X (1.1 equiv), TEA (2.5 equiv), DMF, 90 °C; (2) ≡-J (1.5 equiv), $Cl_2Pd(PPh_3)_2$ (5 mol %), CuI (5 mol %), 55°C. Method E: (1) CH_2═CH−X (1.1 equiv), K_2CO_3 (2 equiv), DMF, 80 °C. 2) $(Bu)_3$-Sn−E (1.5 equiv), $Cl_2Pd(PPh_3)_2$ (5 mol %), 90 °C

Chart 2. Representative Functionality of the Building Blocks (**C**−**E**) Used during Azinone Decoration



and then submitted to the Heck reaction under classical conditions using different catalytic systems (e.g., $Cl_2Pd(PPh_3)_2$, $Pd(OAc)_2$, or $Cl_2Pd[(P(o\text{-Tolyl})_3]_2$). Unfortunately, none of these systems provided significant improvements to the previously described results, and most of the starting adduct (**A4B**) remained unaltered.

Encouraged by the successful results with scaffolds **A1**−**A3** during the aza-Michael/Heck sequence and with the aim of expanding the functional diversity in the heterocyclic backbone, we explored the use of Suzuki, Sonogashira and Stille reactions as consecutive transformations to the initial aza-Michael addition (Scheme 3). A representative selection of the diversity elements incorporated during library production is shown in Chart 2. These were introduced using boronic acids (**C1**−**6**), terminal acetylenes (**D1**−**4**) or stannanes (**E1**−**4**) as reactive precursors (Chart 2); these series have recently been demonstrated[12,13] to be building blocks of paramount importance in combinatorial chemistry because of their commercial availability and potential contribution to library diversity.

The structural decoration of the in situ generated Michael adducts **A1**−**4B** required evaluation of different conditions until the optimal combination for each sequence was found. Standard procedures for each transformation were initially tested, but these conditions were modified to ensure functional group compatibility and to develop high-throughput syntheses that would enable straightforward workup and isolation of products. The catalyst loading used in the experiments was 5 mol %. In all cases, and as previously demonstrated for the aza-Michael/Heck sequence, complete regiochemistry control was easily achieved by using a variable excess (1.5−3 equiv) of the building blocks (**C**−**E**). Optimized conditions are illustrated in Scheme 3.

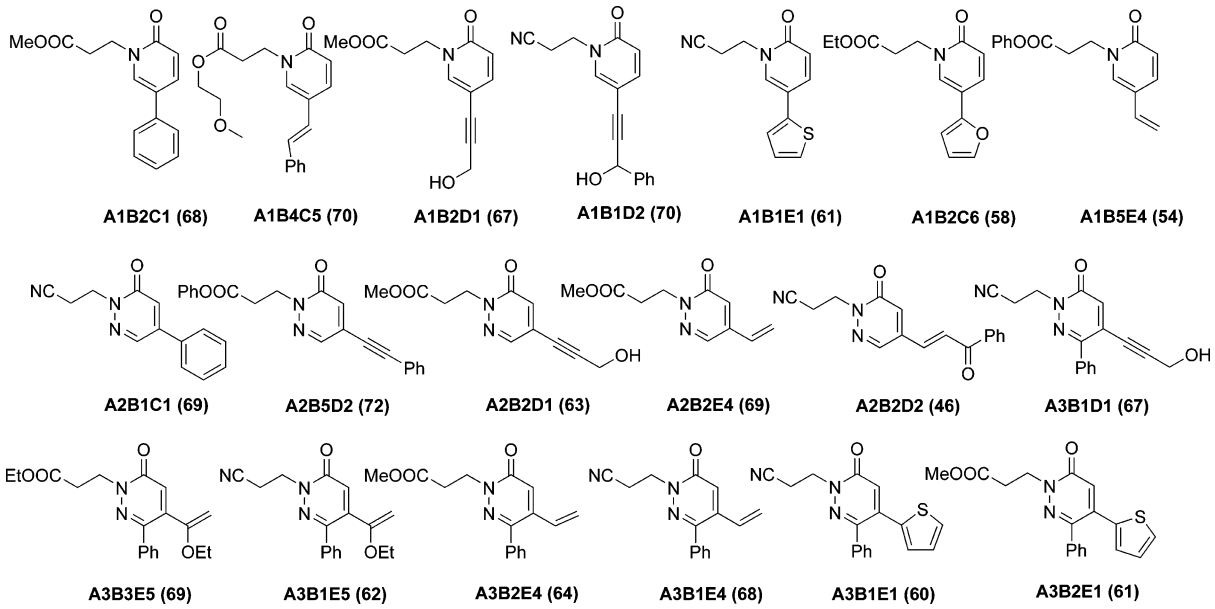
Methyl acrylate (**B2**) and phenyl boronic acid (**C1**) were selected as representative reactive partners to test the viability of the proposed aza-Michael/Suzuki sequence on azinones **A1**−**4**. We were delighted to find that once the base-promoted conjugated addition finished (K_2CO_3/DME/H_2O), addition of **C1**, 5 mol % $Pd(PPh_3)_4$, and heating of the reaction mixture at 90 °C for 1−6 h provided 55−70% overall yield of the desired derivatives (**A1**−**3BC**). The sequence appeared to be of general application and worked well with different Michael acceptors (**B**) and substituted boronic acids (**C**), thus allowing us to prepare a small collection of substituted arylazinones (Chart 3, compounds **A1**−**3BC**).

The one-pot conjugate addition/alkynylation sequence was then investigated. It must be pointed out that, in contrast to recent reports[26] describing elegant and straightforward synthesis of heterocyclic derivatives by one-pot Sonogashira-mediated cross-coupling reactions, in our hands, the development of sequences involving the consecutive addition/alkynylation of the heterocycle were the most difficult (and sometimes even impossible) to optimize. After monitoring the aza-Michael reaction of **A1**−**4** to **B** (K_2CO_3 or TEA in DMF solution) and judging it to be complete, the addition of the corresponding alkyne (**D**) (2 equiv), CuI (5 mol %), palladium catalyst ($Cl_2Pd(PPh_3)_2$ or 10% Pd/C), and heating (55 °C) provided moderate yields (45−70%) of the desired alkynyl azinones. In most experiments, $Cl_2Pd(PPh_3)_2$ proved to be the most effective catalyst. The low yields obtained for scaffold **A3** during the aza-Michael/alkynylation sequence were attributed to the inability of the base (K_2CO_3) to act efficiently on the Michael addition and coupling. We therefore chose to substitute TEA for the K_2CO_3, which proved to be a more effective agent for both processes, increasing the yield of the overall transformation in **A3**.

The preliminary test of the alkyne scope for the aza-Michael/Sonogashira sequence on scaffolds **A1**−**4** allowed preparation of azinones incorporating different alkynyl fragments (e.g., propargyl, phenylethynyl, or phenylpropargyl, Chart 3, compounds **A1**−**3B2D**). According to previous observations[27,28] the use of 1-phenyl-2-propyn-1-ol (**D2**) during Sonogashira coupling may provide the expected phenyl propynols (e.g. **A1B2D2**) or their isomeric heterocyclic chalcones (e.g., **A2B1D2**). The findings presented here (**A1B2D2** compared with **A2B2D2**) are fully consistent with the previous evidence,[28] confirming that such a base-promoted isomerization is strongly favored in highly electron-deficient halides (e.g., **A2** and **A3**).

Investigation of the feasibility of the aza-Michael/Stille sequence in **A1**−**4** was begun by surveying the effect of different catalysts and temperatures during the coupling of stannanes **E** to the adducts **AB**. This preliminary study was considerably simplified by the fact that Stille reaction does not require the presence of a base. In accordance, only one

Chart 3. Representative Structure of Diversely Functionalized Azinones Produced[a,b]



[a] Yields are shown in parentheses.[20] [b] Reported yields refer to the mean of at least two different experiments.

equivalent of K_2CO_3 was used to facilitate the conjugate addition to the Michael acceptor. Once the conjugate addition was finished (4−6 h), the corresponding stannane **E** (1.5 equiv) and catalyst $[Cl_2Pd(PPh_3)_2]$ were added, and the reaction mixture was heated (80 °C) for 4−8 h to yield moderate amounts of **A1**−**3BE** (Chart 3).

Although Schemes 2 and 3 show optimized experimental parameters for proposed sequences that yield moderate to satisfactory amounts of the targeted structures, it should be pointed out that even when using iododerivatives, concomitant formation of homocoupling products (4−10%) was detected in most of transformations.

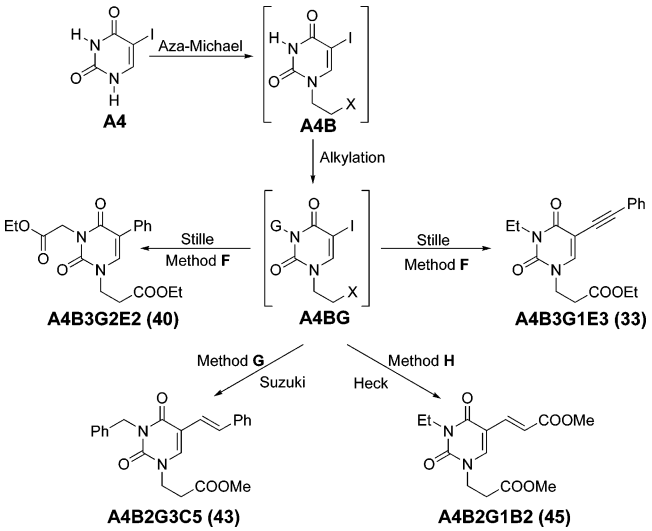
In sharp contrast to the success accomplished with pyridin-2(1*H*)-ones (**A1**) and pyridazin-3(2*H*)-ones (**A2** and **A3**), no such success was achieved with uracil **A4** when conjugate addition was followed consecutively by the Suzuki, Sonogashira, or Stille reaction (as described for the aza-Michael/Heck sequence). Unfortunately, efforts to obtain at least modest yields by modification of the reaction partner [e.g., boronic acid (**C**), acetylene (**D**), or stannane (**E**)], temperature, reaction times, and type or amount of catalyst remained ineffectual. This finding is in contrast with the well-documented reactivity of 1-alkyl-5-halopyridin-2,4(1*H*,3*H*)-diones[29] and uracil nucleosides[30] in cross-coupling reactions. However, in light of our own experience with palladium-catalyzed reactions on 5-halopyridazin-3(2*H*)-ones,[31] such failure is not completely unexpected and may be attributed to the reactivity of the tautomeric heterocyclic NH group of the lactame functionality. Indeed, interference of the NH−CO functionality during Sonogashira couplings in 4-halopyridazin-3(2*H*)-ones, 5-halopyrimidin-4(3*H*)-ones, or 5-halopyrimidin-2,4(3*H*)-diones have been reported[26] and attributed to intramolecular nucleophilic addition of the enol tautomer to the highly reactive acetylenic residue. Exploitation of this reactivity has allowed the straighforward preparation of bicyclic derivatives[32,33] (e.g. furo[2,3-*c*]pyridazines or furo-[2,3-*d*]pyrimidines).

The failures experienced regarding the use of uracils (**A4**−**A6**) in the proposed consecutive aza-Michael/palladium-catalyzed transformations strongly decreased the desired skeletal diversity of the library (Charts 1 and 3). Such deficiency is even more important when the paramount importance and prevalence of uracil scaffolds in nature and in pharmacologically active substances[11] are taken into consideration. Thus, in a final effort to overcome these drawbacks, we considered the possibility of preventing interference by NH, by introducing an alkyl group at the nitrogen atom (N-3) before carrying out the cross-coupling reactions. If successful, such blockage would be formally considered as another point of diversity on the heterocyclic core. Our specific goal was to extend a recently reported[13] consecutive alkylation/palladium-catalyzed sequence (which was shown to work fairly well for 1-substituted uracils) to the results described here on Michael adducts **A4B**. The proposed approach would comprise three consecutive reactions on **A4** involving the initial regioselective (N-1) aza-Michael addition; the selective alkylation at N-3; and finally, the structural diversification of position 5 by a cross-coupling reaction on the iodo atom of the heterocyclic base (Scheme 4).

For proof of concept, the in situ-generated adducts **A4B** were submitted to reaction with different alkyl halides (**G**) [e.g., methyl iodide (**G1**), ethyl bromide (**G2**), benzyl bromide (**G3**), or ethyl bromoacetate (**G4**)] in the presence of basic conditions (K_2CO_3) at 70 °C; complete consumption of the adduct was observed after 2−4 h. Comparison with authentic samples confirmed the efficiency of such a highly selective sequence. With this valuable information, we were then ready to evaluate the performance of the proposed one-pot three-step sequential transformations on **A4** (Scheme 4).

Under optimal conditions, the sequences involving the cross-coupling reaction with phenyltributyl stannane (**E2**), methyl acrylate (**B2**), phenylvinylboronic acid (**C5**), or tributylphenylethynyl stannane (**E3**) as a final step

Scheme 4. One-Pot Consecutive Aza-Michael/Alkylation/ Palladium-Catalyzed Functionalization on 5-Iodopyrimidine-2,4(1*H*,3*H*)-dione **A4**[a]



[a] Method F: (1) CH_2═CH−X (1.1 equiv), K_2CO_3 (2.5 equiv), MeCN−H_2O, 40 °C; (2) G (1.5 equiv), 70 °C; (3) $(Bu)_3$-Sn−E (2 equiv), $Cl_2Pd(PPh_3)_2$ (5 mol %), 80 °C. Method G: (1) CH_2═CH−X (1.1 equiv), K_2CO_3 (2.5 equiv), DME/H_2O, 40 °C; (2) G (1.5 equiv), 70 °C; (3) Ar−$B(OH)_2$ (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), 90 °C. Method H: (1) CH_2═CH−X (1.1 equiv), K_2CO_3 (2.5 equiv), MeCN/H_2O, 40 °C; (2) G (1.5 equiv), 70 °C. 3) CH_2═CH−X (2 equiv), 10% Pd/C (5 mol %), 110 °C.

reached completion within 16−24 h, yielding reasonable amounts (43−68%) of the desired derivatives (**A4B3G2E2**, **A4B3G1E3**, **A4B2G3C5**, **A4B2G1B2**). The combinatorial exploitation of the developed sequences is currently in progress.

The scope of this methodology involving the synthesis of some representative elements of the targeted pyrimidino-2,4-diones incorporating three points of diversity (1, 3, and 5) is illustrated in Scheme 4. For most transformations, the experimental protocols were very similar to those sequences previously developed for **A1**−**A3**, with the only exception being the sequences with the Stille coupling as the final process, which did not work well in the presence of water (required as a cosolvent to accelerate the aza-Michael addition using K_2CO_3 as base). We therefore opted to remove H_2O once alkylation was completed by incubation of the reaction mixture with diatomaceous earth and then filtration and, finally, submitting the filtrate to reaction with the proper stannane (**E**) and catalyst.

Disappointingly, we have not, to date, established the experimental conditions allowing sequential completion of the one-pot structural diversification of uracil **A4** at N-1 (aza-Michael) and N-3 (alkylation) with the alkynylation of position 5 by a Sonogashira cross-coupling reaction. One possible explanation for this unsuccessful result may be the interference of the cocatalyst (CuI) required in Sonogashira coupling. Despite this limitation, the under-represented chemical space of alkynyl uracils (**A4BGE**) has been compensated, at least in part, by the excellent potential that the Stille reaction offers in terms of diversity (Scheme 4, compound **A4B3G1E3**).

In view of the observed strict control exercised by the electron-deficient olefins during the aza-Michael process and the minor reactivity of azinones with a free NH group in palladium-catalyzed reactions, as compared with *N*-alkyl azinones, the conceptual possibility of performing these sequences in a three-component reaction (3-CR) was examined. This worked satisfactorily for the simplest sequence involving the aza-Michael/Heck reaction but, unfortunately, produced an important decrease in regiocontrol for the other transformations, even when a large excess of **B**, **C**, **D,** or **E** was used.

In summary, we have documented several new sequential one-pot three-component coupling approaches that are initiated by straightforward and highly regioselective addition of an azinone (**A**) to the α,β-unsaturated system of a Michael acceptor (**B**). The methodology provides simple and convergent access to valuable, highly diverse, and functionalized azinone libraries, and is particularly well-suited for combinatorial development. The broad scope of the developed sequence has been preliminary demonstrated by using different commercially available Michael acceptors (**B**) and a collection of skeletal diverse azinones (**A**) and, most importantly, by the wide range of functionality incorporated into libraries by the use of Heck, Suzuki, Sonogashira, or Stille reactions. This evidence confirms the reported consecutive transformations as attractive methodologies for lead identification/optimization processes as well as a source of new functionalized exclusive library scaffolds for libraries from library approaches.

Further work is in progress to study the use of other Michael acceptors [including olefins containing sulfur-based electron-withdrawing groups and solid supported reagents (e.g. REM resin)] and also to implement the full range of combinatorial applicability of the present approach by employing supported reagents and scavengers.

Experimental Section

General Details. Commercially available starting materials and reagents were purchased and used without further purification. Reactions were usually carried out on a 10-mmol scale and run to (near) completion. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured using a Perkin-Elmer 1640 FT-IR spectrophotometer with samples incorporated in potassium bromide pellets. The NMR spectra were recorded on Bruker AM300 and XM500 spectrometers. Chemical shifts are given as δ values against tetramethylsilane as internal standard, and J values are given in Hz. Mass spectra were obtained on a Varian MAT-711 instrument. High-resolution mass spectra were obtained on an Autospec Micromass spectrometer. The reactions were monitored by TLC with 2.5-mm Merck silica gel GF 254 strips, and each of the purified compounds showed a single spot. Unless stated otherwise, iodine vapor, UV light, or both were used for detection of compounds. The synthesis, isolation, and purification of compounds were accomplished using equipment routinely available in laboratories for parallel synthesis. A PLS (6 × 4) organic synthesizer was used for compound preparation; isolation of precipitated/triturated products was performed in a 12-channel vacuum manifold from Aldrich that was fitted with Aldrich Bond-

Elut reservoirs. Solvent removal was achieved using standard techniques or an evaporation module from Advanced Chemtech. All compounds described were purified by recrystallization from suitable solvents or by chromatographic methods (column or preparative) to obtain analytically pure samples.

Synthesis of Aza-Michael Adducts AB. General Procedure. First, the base (TEA or K_2CO_3) (2 mmol) and then the corresponding Michael acceptor (**B**) (1.1 mmol) were added to a solution of the azinone **A** (1 mmol) in the proper solvent (DMF, CH_3CN/H_2O (3:1), or DME/H_2O(3:1)) (4 mL). The mixture was stirred and heated (80 °C for scaffolds **A1**, **A2**, and **A3**; 40 °C for **A4**) until the starting material was consumed (1−8 h). After cooling, the solvent was evaporated. For those reactions performed in the presence of water, the mixture was diluted with 2 mL of the other solvent (DME or CH_3CN) and stirred for 10 min with diatomaceous earth, filtered, and washed, and the filtrate was evaporated to dryness. Purification by recrystallization or column chromatography yielded the desired Michael adducts **AB** as analytically pure samples.

3-(5-Iodo-2-oxo-2*H*-pyridin-1-yl)-propionic Acid 2-Methoxyethyl Ester (A1B4). Purification by column chromatography using AcOEt/hexane (1:2) as eluent afforded a solid. Yield 92%. IR (KBr): ν_{max}/cm^{-1} 1733 (CO), 1650 (CO), 1573 (aromatics). ^1H NMR ($CDCl_3$,, 300 MHz), δ (ppm): 7.65 (d, $J = 2.5$ Hz, 1H, CH), 7.40 (dd $J = 2.5$, $J = 9.5$ Hz, 1H, CH), 6.32 (d, $J = 9.5$ Hz, 1H, CH), 4.20 (t, $J = 4.6$ Hz, 2H, CH_2), 3.82 (t, $J = 6.2$ Hz, 2H, CH_2), 3.54 (t, $J = 4.6$ Hz, 2H, $-CH_2$), 3.34 (s, 3H, CH_3), 2.83 (t, $J = 6.2$ Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 171.6, 161.3, 147.6, 144.0, 122.9, 70.5, 64.4, 64.3, 59.4, 46.7, 33.2. MS (70 eV) *m*/*z* (%): 351 (M^+, 2), 293 (15), 248 (10), 221 (30), 55 (30), 55 (100). HRMS (EI): $C_{11}H_{14}INO_4$ calcd, 350.9968; found, 351.0005.

3-(4-Iodo-6-oxo-6*H*-pyridazin-1-yl)-propionitrile (A2B1). Purification by column chromatography using AcOEt/hexane (1:1) as eluent afforded a white solid. Yield: 95%, mp 58−60 °C (MeOH). IR (KBr): ν_{max}/cm^{-1} 2252 (C≡N), 1663 (CO), 1590 (aromatics). ^1H NMR ($CDCl_3$ 75 MHz), δ (ppm): 7.94 (d, $J = 1.9$, 1H, H_6), 7.45 (d, $J = 1.9$, 1H, H_4), 4.33 (t, $J = 6.7$ Hz, 2H, CH_2), 2.86 (t, $J = 6.7$ Hz, 2H, CH_2).^{13}C NMR ($CDCl_3$, 300 MHz), δ (ppm): 158.7, 143.1, 138.7, 117.1, 103.7, 47.6, 16.8. MS (70 eV) *m*/*z* (%): 275 (M^+, 22), 222 (82), 165 (100). HRMS (EI): $C_7H_6IN_3O$ calcd, 274.9556; found, 275.9571.

3-(4-Iodo-6-oxo-6*H*-pyridazin-1-yl)-propionic Acid Methyl Ester (A2B2). Purification by column chromatography using AcOEt/hexane (1:1) as eluent afforded a solid. Yield 98%. IR (KBr): ν_{max}/cm^{-1} 1730 (COO), 1640 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.91 (d, $J = 1.9$ Hz, 1H, H_6), 7.46 (d, $J = 1.9$ Hz, 1H, H_4), 4.38 (t, $J = 7.1$ Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 2.81 (t, $J = 7.1$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 171.6, 158.9, 142.3, 138.6, 103.0, 52.3, 47.7, 32.6. MS (70 eV) *m*/*z* (%): 308 (M^+, 34), 249 (49), 222 (100). HRMS (EI) $C_8H_9IN_2O_3$ calcd, 307.9658; found, 307.9660.

3-(4-Bromo-6-oxo-3-phenyl-6*H*-pyridazin-1-yl)-propionitrile (A3B1). Purification by column chromatography using AcOEt/hexane (1:5) as eluent afforded a solid. Yield 97%, mp 102−103 °C (MeOH). IR (KBr): ν_{max}/cm^{-1} 2250 (CN), 1658 (CO), 1598 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.56 (m, 2H, aromatics), 7.46 (m, 3H, aromatics), 7.39 (s, 1H, H_4), 4.43 (t, $J = 7.1$ Hz, 2H, $-CH_2$), 2.91 (t, $J = 7.1$ Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 158.5, 147.4, 134.7, 133.1, 131.1, 130.1, 129.6, 128.6, 117.1, 47.6, 16.9. MS (70 eV) *m*/*z* (%): 304 (M^+, 25), 193 (48), 114 (100), 51 (62). HRMS (EI): $C_{13}H_{10}BrN_3O$ calcd, 303.0007; found, 303.0010.

3-(4-Bromo-6-oxo-3-phenyl-6*H*-pyridazin-1-yl)-propionic Acid Methyl Ester (A3B2). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 97%. IR (KBr): ν_{max}/cm^{-1} 1734 (CO), 1655 (CO), 1597 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.50 (m, 2H, aromatics), 7.45 (m, 3H, aromatics), 7.35 (s, 1H, H_4), 4.46 (t, $J = 7.1$ Hz, 2H, $-CH_2$), 3.64 (s, 1H, CH_3), 2.82 (t, $J = 7.1$ Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.6, 158.7, 146.5, 135.1, 132.9, 129.8, 129.6, 129.2, 128.5, 52.2, 47.6, 32.8. MS (70 eV) *m*/*z* (%): 337 (M^+, 6), 236 (31), 193 (35), 114 (100), 50 (74). HRMS (EI): $C_{14}H_{13}BrN_2O_3$ calcd, 331.0110; found, 331.0114.

3-(4-Bromo-6-oxo-3-phenyl-6*H*-pyridazin-1-yl)-propionic Acid Ethyl Ester (A3B3). Purification by column chromatography using AcOEt/hexane (1:5) as eluent afforded a solid. Yield 94%. IR (KBr): ν_{max}/cm^{-1} 1734 (COO), 1664 (CO), 1578 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.49 (m, 2H, aromatics), 7.44 (m, 3H, aromatics), 7.34 (s, 1H, H_4), 4.46 (t, $J = 7.1$ Hz, 2H, CH_2), 4.22 (q, $J = 7.1$ Hz, 2H, CH_2), 2.83 (t, $J = 7.1$ Hz, 2H, $-CH_2$), 1.17 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.1, 158.7, 146.5, 135.1, 132.9, 130.1, 129.8, 129.6, 128.5, 61.1, 47.7, 33.0, 14.4. MS (70 eV) *m*/*z* (%): 350 (M^+, 11), 236 (100), 193 (50), 114 (65). HRMS (EI): $C_{15}H_{15}BrN_2O_3$ calcd, 350.0266; found, 350.0270.

3-(5-Iodo-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-propionic Acid Methyl Ester (A4B2). Purification by column chromatography using AcOEt/hexane (1:1) as eluent afforded a solid. Yield 93%, mp 181−182 °C (*i*-PrOH). IR (KBr): ν_{max}/cm^{-1} 1728 (CO), 1707 (CO), 1643 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 11.61 (bs, 1H, NH), 8.15 (s, 1H, CH), 3.88 (t, $J = 6.7$ Hz, 2H, $-CH_2$), 3.58 (s, 1H, $-CH_3$), 2.68 (t, $J = 6.7$ Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.5, 161.4, 150.9, 150.7, 68.1, 51.9, 44.4, 32.7. MS (70 eV) *m*/*z* (%): 324 (M^+, 21), 264 (7), 238 (6), 208 (11), 127 (59), 59 (100). HRMS (EI): $C_8H_9IN_2O_4$ calcd, 323.9607; found, 323.9612.

3-(5-Iodo-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-propionic Acid Ethyl Ester (A4B3). Purification by column chromatography using AcOEt/hexane (1:1) as eluent afforded a solid. Yield 94%, mp 159−160 °C (*i*-PrOH). IR (KBr): ν_{max}/cm^{-1} 1727 (CO), 1681 (CO), 1652 (CO). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 11.70 (bs, 1H, NH), 8.14 (s, 1H, CH), 4.05 (q, $J = 7.1$ Hz, 2H, CH_2), 3.88 (t, $J = 6.7$ Hz, 2H, $-CH_2$), 2.66 (t, $J = 6.7$ Hz, 2H, $-CH_2$), 1.16 (t, $J = 7.1$ Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.0, 161.5, 151.0, 150.7, 68.1, 60.5, 44.5, 33.0, 14.4. MS (70 eV) *m*/*z* (%): 338 (M^+, 1), 238 (16), 208 (25), 165 (35), 127 (100), 55 (74). HRMS (EI): $C_9H_{11}IN_2O_4$ calcd, 337.9764; found, 337.9769.

General Procedure for the Aza-Michael/Heck Sequence on A1−3 (Methods A and B). A mixture of the azinone **A** (1.0 mmol), the corresponding Michael acceptor (**B**) (1.0 mmol), and base (2.5 mmol) (K_2CO_3 for **A1**−**A2** or TEA for **A3**) in 2.5 mL of MeCN (**A1** and **A2**) or DMF (**A3**) was stirred and heated (80 °C) under argon until the starting material was consumed (30−60 min). After cooling, the palladium catalyst (5 mol %) (10% Pd/C for **A1** and **A2** or $Cl_2Pd(PPh_3)_2$ for **A3**) and the corresponding olefin (1.5 mmol) were added. The mixture was heated (90 °C) for 2−6 h, allowed to cool at room temperature, filtered through a Celite pad, and washed (AcOEt, 3 times), and the filtrate was evaporated to dryness to give a residue that was purified by column chromatography (silica gel) to obtain analytically pure samples.

3-[6-Oxo-1-(2-phenoxycarbonylethyl)-1,6-dihydropyridin-3-yl]-acrylic Acid Phenyl Ester (A1B5B5). Purification by column chromatography using AcOEt/hexane (1:2) as eluent afforded a solid. mp 157−158 °C (EtOH). Yield 78%. IR (KBr): ν_{max}/cm^{-1} 1754 (CO), 1720 (CO), 1654 (CO), 1589 (aromatics). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.73 (d, J = 2.3 Hz, 1H, CH), 7.67 (d, J = 9.5 Hz, 1H, CH), 7.56 (d, J = 15.8 Hz, 1H, CH), 7.37 (m, 5H, aromatics), 7.14 (m, 5H, aromatics), 7.03 (d, J = 7.8 Hz, 1H, CH), 6.64 (d, J = 9.5 Hz, 1H, CH), 6.30 (d, J = 15.8 Hz, 1H, CH), 3.43 (t, J = 5.8 Hz, 2H, CH_2), 3.16 (t, J = 5.8 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 170.6, 165.5, 162.4, 151.1, 150.6, 142.4, 141.8, 136.8, 129.9, 129.8, 126.5, 126.1, 121.9, 121.8, 121.7, 115.0, 114.5, 47.1, 33.1. MS (EI) *m*/*z* (%): 390 (M$^+$, 53), 296 (46), 94 (100).

3-[1-(2-Methoxycarbonylethyl)-6-oxo-1,6-dihydropyridazin-4-yl]-acrylic Acid Methyl Ester (A2B2B2). Purification by column chromatography using AcOEt/hexane (1:2) as eluent afforded a solid, mp 120−122 °C (*i*-PrOH). Yield 65%. IR (KBr): ν_{max}/cm^{-1} 1733 (COO), 1636 (CO). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.89 (d, J = 2.1 Hz, 1H, H_6), 7.40 (d, J = 16.1 Hz, 1H, CH), 6.90 (d, J = 2.1 Hz, 1H, H_4), 6.53 (d, J = 16.1 Hz, 1H, CH), 4.41 (t, J = 7.0 Hz, 1H, H_2), 3.82 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 2.83 (t, J = 7.0 Hz, 1H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.7, 165.9, 160.3, 138.2, 134.3, 128.2, 125.5, 52.7, 52.3, 47.8, 32.8, 31.3. MS (70 eV) *m*/*z* (%): 266 (M$^+$, 55), 234 (45), 207 (40), 179 (100). HRMS *m*/*z* calcd, for $C_{12}H_{14}IN_2O_5$ (M$^+$): 266.0903; found, 266.0907.

3-[1-(2-Cyanoethyl)-6-oxo-3-phenyl-1,6-dihydropyridazin-4-yl]-acrylonitrile (A3B1B1). Purification by column chromatography using AcOEt/hexane (1:5) as eluent afforded a solid. Yield 68%. IR (KBr): ν_{max}/cm^{-1} 2252 (CN), 1658 (CO). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.47 (m, 6H, 5H aromatics + 1H, CH), 7.26 (s, 1H, H_4), 5.96 (d, J = 16.4 Hz, 1H, −CH), 4.51 (t, J = 7.1 Hz, 2H, $-CH_2$), 2.97 (t, J = 7.1 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75.5 MHz), δ (ppm): 159.8, 145.6, 144.7, 138.6, 133.9, 130.3, 129.4, 129.2, 127.5, 116.5, 115.5, 104.7, 48.0, 17.1. MS (70 eV) *m*/*z* (%): 276 (M$^+$, 24), 222 (81), 166 (100), 139 (52), 51 (77).

3-[1-(2-Ethoxycarbonylethyl)-6-oxo-3-phenyl-1,6-dihydropyridazin-4-yl]-acrylic Acid Ethyl Ester (A3B3B3). Purification by column chromatography using AcOEt/hexane (1:5) as eluent afforded a solid. Yield 63%. IR (KBr): ν_{max}/cm^{-1} 1726 (COO), 1658 (CO). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.39 (m, 6H, 5H aromatics + 1H, CH), 7.09 (s, 1H, H_4), 6.41 (d, J = 15.8 Hz, 1H, −CH), 4.52 (t, J = 7.1 Hz, 2H, $-CH_2$), 4.24 (q, J = 7.0 Hz, 2H, $-CH_2$), 4.12 (q, J = 7.1 Hz, 2H, $-CH_2$), 2.87 (t, J = 7.0 Hz, 2H, $-CH_2$), 1.29 (t, J = 7.1 Hz, 3H, $-CH_3$), 1.19 (t, J = 7.1 Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.3, 165.6, 159.9, 146.2, 139.1, 139.0, 134.6, 129.8, 129.3, 119.0, 126.6, 125.9, 61.5, 61.1, 47.7, 33.1, 14.5, 14.5. MS (70 eV) *m*/*z* (%): 370 (M$^+$, 100), 296 (77), 256 (64), 138 (100), 115 (62), 55 (93), 26 (98).

3-[1-(2-Cyanoethyl)-6-oxo-1,6-dihydropyridin-3-yl]-acrylic Acid Methyl Ester (A1B1B2). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. mp 168−169 °C (MeOH). Yield 61%. IR (KBr): ν_{max}/cm^{-1} 2214 (C≡N), 1707 (CO), 1660 (CO), 1598 (aromatics). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.64 (d, J = 9.5 Hz, 1H, CH), 7.53 (s, 1H, CH), 7.42 (d, J = 15.8 Hz, 1H, −CH), 6.62 (d, J = 9.5 Hz, 1H, CH), 6.16 (d, J = 15.8 Hz, 1H, −CH), 4.17 (t, J = 6.4 Hz, 2H, $-CH_2$), 3.78 (s, 3H, $-CH_3$), 2.92 (t, J = 6.4 Hz, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 167.5, 162.7, 140.0, 139.5, 137.4, 122.0, 117.2, 116.5, 115.3, 52.2, 47.1, 17.7. MS (70 eV) *m*/*z* (%): 232 (M$^+$, 100), 201 (61), 179 (86), 140 (96), 118 (35).

3-(2-Oxo-5-styryl-2*H*-pyridin-1-yl)-propionic Acid 2-Methoxyethyl Ester (A1B4B6). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 55%. IR (KBr): ν_{max}/cm^{-1} 1733 (CO), 1661 (CO), 1595 (aromatics). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.67 (d, J = 9.4 Hz, 1H, CH), 7.50 (d, J = 2.5 Hz, 1H, CH), 7.42 (m, 2H, aromatics), 6.61 (d, J = 9.4 Hz, 1H, CH), 4.23 (t, J = 4.6 Hz, 2H, CH_2), 4.18 (t, J = 6.1 Hz, 2H, CH_2), 3.55 (d, J = 4.6 Hz, 1H, CH), 3.34 (s, 3H, CH_3), 2.90 (t, J = 6.1 Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.8, 162.4, 137.7, 137.2, 129.1, 129.0, 128.0, 127.1, 126.5, 123.6, 121.3, 117.7, 70.6, 64.3, 59.3, 46.9, 33.3. MS (70 eV) *m*/*z* (%): 327 (M$^+$, 33), 269 (25), 225 (20), 197 (65), 115 (40), 55 (100).

3-[1-(2-Methoxycarbonylethyl)-6-oxo-1,6-dihydropyridazin-4-yl]-acrylic Acid Ethyl Ester (A2B2B3). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 54%. mp 143−145 °C (*i*-PrOH). IR (KBr): ν_{max}/cm^{-1} 1731 (CO), 1660 (CO). ^{1}H NMR ($CDCl_3$, 75 MHz), δ (ppm): 7.89 (d, J = 2.1 Hz, 1H, H_6), 7.44 (d, J = 16.1 Hz, 1H, CH), 6.09 (d, J = 2.1 Hz, 1H, H_4), 7.89 (d, J = 16.1 Hz, 1H, CH), 4.42 (q, J = 7.1 Hz, 2H, CH_2), 4.25 (t, J = 6.9 Hz, 2H, CH_2), 3.66 (s, 3H, CH_3), 2.82 (t, J = 6.9 Hz, 2H, CH_2), 1.31 (t, J = 7.1 Hz, 3H, CH_3).^{13}C NMR ($CDCl_3$, 300 MHz), δ (ppm): 171.5, 165.5, 160.3, 137.9, 137.4, 134.3, 128.1, 126.0, 61.7, 52.3, 47.7, 32.9, 14.6. MS (70 eV) *m*/*z* (%): 280 (M$^+$, 48), 234 (41), 194 (100), 147 (38).

3-(6-Oxo-3-phenyl-4-styryl-6*H*-pyridazin-1-yl)-propionitrile (A3B1B6). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 63%, mp 185−186 °C (MeOH). IR (KBr): ν_{max}/cm^{-1} 2250 (CN), 1656 (CO), 1594 (aromatics). ^{1}H NMR ($CDCl_3$, 300

MHz), δ (ppm): 7.52 (m, 5H, aromatics), 7.35 (m, 5H, aromatics), 7.18 (s, 1H, −CH), 7.16 (d, J = 16.1 Hz, 1H, CH), 6.79 (d, J = 16.1 Hz, 1H, CH), 4.52 (t, J = 6.7 Hz, 2H, $-CH_2$), 2.96 (t, J = 6.7 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.4, 147.8, 142.5, 136.9, 135.9, 134.9, 129.8, 129.8, 129.5, 129.3, 129.0, 127.4, 123.6, 122.7, 117.4, 47.5, 17.1. MS (70 eV) *m*/*z* (%): 327 (M^+, 7), 273 (9), 215 (37), 202 (21), 139 (21), 115 (41), 54 (100).

General Procedure for the Aza-Michael/Suzuki Sequence on A1−3 (Method C). A mixture of the corresponding Michael acceptor (**B**) (1.0 mmol), azinone **A** (1.0 mmol), and K_2CO_3 (3.0 mmol), in DME/H_2O (3:1, 3 mL) was stirred and heated (80 °C) under argon until complete consumption of **A** (30 min to 1 h). After cooling to room temperature, the corresponding boronic acid (**C**) (2.2 mmol) and $Pd(PPh_3)_4$ (0.016 mmol) were added. The mixture was heated (80 °C) for 8−12 h. The obtained solution was filtered through a Celite pad and washed (DME, 3 times), and the filtrate was evaporated to dryness to give a residue that was then purified by column chromatography (silica gel or crystallization) to obtain analytically pure samples.

3-(2-Oxo-5-phenyl-2*H*-pyridin-1-yl)-propionic Acid Methyl Ester (A1B2C1). Purification by column chromatography using AcOEt/hexane (1:1) as eluent afforded a yellow oil. Yield 68%. IR (KBr): ν_{max}/cm^{-1} 1728 (CO), 1662 (CO), 1594 (aromatics). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.64 (m, 3H, aromatics + CH), 7.40 (m, 4H, aromatics + CH), 6.62 (d, J = 9.4 Hz, 1H, CH), 4.18 (t, J = 6.1 Hz, 2H, $-CH_2-$), 3.64 (s, 3H, $-CH_3$), 3.67 (s, 3H, $-CH_3$), 2.87 (t, J = 6.1 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 172.3, 162.2, 140.0, 136.8, 136.5, 129.4, 127.6, 126.1, 121.1, 120.3, 52.4, 47.0, 33.2. MS (70 eV) *m*/*z* (%): 257 (M^+, 100), 198 (48), 171 (42), 118 (34).

3-(2-Oxo-5-styryl-2*H*-pyridin-1-yl)-propionic Acid 2-Methoxyethyl Ester (A1B4C5). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 70%. Also obtained by the aza-Michael/Heck sequence employing styrene (**B6**) as olefin partner (compound **A1B4B6**)

3-(6-Oxo-4-phenyl-6*H*-pyridazin-1-yl)-propionitrile (A2B1C1). Purification by column chromatography using AcOEt/hexane (1:2) as eluent afforded a yellow oil. Yield: 64%. IR (KBr): ν_{max}/cm^{-1} 2250 (C≡N), 1661 (CO), 1596 (aromatics). ^{1}H NMR ($CDCl_3$, 75 MHz), δ (ppm): 8.10 (d, J = 2.2, 1H, H_6), 7.56 (m, 2H, aromatics), 7.51 (m, 3H, aromatics), 7.05 (d, J = 2.2, 1H, H_4), 4.46 (t, J = 6.7 Hz, 2H, CH_2), 2.94 (t, J = 6.7 Hz, 2H, CH_2).^{13}C NMR ($CDCl_3$, 300 MHz), δ (ppm): 160.6, 144.7, 137.1, 133.9, 130.9, 129.8, 127.3, 124.9, 117.4, 47.6, 16.9. MS (70 eV) *m*/*z* (%): 225 (M^+, 12), 172 (50), 115 (100).

3-(6-Oxo-3,4-diphenyl-6*H*-pyridazin-1-yl)-propionitrile (A3B1C1). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 64%. IR (KBr): ν_{max}/cm^{-1} 2249 (CN), 1710 (CO), 1662 (CO), 1590 (aromatics). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.28 (m, 6H, aromatics), 7.20 (m, 2H, aromatics), 7.10 (m, 2H, aromatics), 6.95 (s, 1H, H_4), 4.53 (t, J = 6.7 Hz, 2H, $-CH_2$), 2.98 (t, J = 6.7 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.1, 147.3, 146.7, 135.9, 135.5, 129.6, 129.5, 129.3, 129.2, 129.0, 128.9, 128.5, 117.5, 47.5, 17.1. MS (70 eV) *m*/*z* (%): 301 (M^+, 32), 247 (68), 191 (100), 102 (27), 51 (64).

3-(6-Oxo-3-phenyl-4-styryl-6*H*-pyridazin-1-yl)-propionitrile (A3B1C5). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 64%. Also obtained by the aza-Michael/Heck sequence employing styrene (**B6**) as olefin partner (compound **A3B1B6**).

General Procedure for the Aza-Michael/Sonogashira Sequence on A1−3 (Method D). A mixture of azinone **A** (1.0 mmol), the corresponding Michael adduct (**B**) (1.0 mmol), and Et_3N (3.0 mmol) in DMF (2.5 mL) was stirred and heated (90 °C) under argon until the starting material (**A**) was consumed (30−60 min). After cooling, $PdCl_2(PPh_3)_2$ (0.05 mmol), CuI (0.05 mmol), and the corresponding terminal acetylene (**D**) (1.5 mmol) were added. The mixture was heated (55 °C) for 4−8 h, then cooled to room temperature, diluted with dichloromethane, filtered through a Celite pad, and washed (AcOEt, 3 times). The filtrate was evaporated to dryness, and the residue obtained was purified by column chromatography (silica gel) to obtain analytically pure samples.

3-[5-(3-Hydroxyprop-1-ynyl)-2-oxo-2*H*-pyridin-1-yl]-propionic Acid Methyl Ester (A1B2D1). Purification by column chromatography using AcOEt/hexane (2:1) as eluent afforded a solid. Yield 70%. IR (KBr): ν_{max}/cm^{-1} 2354 (C≡C), 1727 (CO), 1661 (CO), 1591 (aromatics). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.59 (d, J = 2.3 Hz, CH), 7.26 (d, J = 9.4 Hz, 1H, CH), 7.46 (d, J = 9.4 Hz, 1H, CH), 4.38 (s, 2H, $-CH_2-$), 4.13 (t, J = 6.1 Hz, 2H, $-CH_2-$), 3.64 (s, 3H, $-CH_3$), 2.92 (s, 1H, OH), 2.81 (t, J = 6.1 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 172.1, 161.8, 142.8, 142.6, 120.8, 102.5, 88.9, 80.8, 52.3, 51.5, 47.1, 32.8. MS (70 eV) *m*/*z* (%): 235 (M^+, 100), 204 (18), 176 (57), 149 (32).

3-[5-(3-Hydroxy-3-phenylprop-1-ynyl)-2-oxo-2*H*-pyridin-1-yl]-propionitrile (A1B1D2). Purification by column chromatography using AcOEt/hexane (2:1) as eluent afforded a solid. Yield 70%. IR (KBr): ν_{max}/cm^{-1} 3322 (OH), 2251 (C≡C), 2224 (C≡C), 1665 (CO), 1594 (aromatics). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.89 (s, 1H, CH), 7.50 (m, 3H, aromatics), 7.32 (d, J = 8.6 Hz, 1H, CH), 7.28 (m, 2H, aromatics), 6.45 (d, J = 9.3 Hz, CH), 5.57 (s, 1H, −CH−), 4.40 (bs, 1H, OH), 4.01 (t, J = 6.3 Hz, 2H, $-CH_2-$), 2.77 (t, J = 6.3 Hz, 2H, $-CH_2-$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 161.5, 143.2, 141.7, 141.3, 128.9, 128.6, 126.9, 120.9, 117.5, 103.3, 91.3, 80.9, 64.6, 46.8, 17.3. MS (70 eV) *m*/*z* (%): 278 (M^+, 91), 225 (65), 196 (100), 181 (36), 152 (17), 105 (29).

3-[4-(3-Hydroxyprop-1-ynyl)-6-oxo-6*H*-pyridazin-1-yl]-propionic Acid Methyl Ester (A2B2D1). Purification by column chromatography using AcOEt/hexane (2:1) as eluent afforded a solid. Yield 63%. IR (KBr): ν_{max}/cm^{-1} 2228 (C≡C), 1731 (CO), 1651 (CO). ^{1}H NMR ($CDCl_3$, 75 MHz), δ (ppm): 7.66 (d, J = 1.9 Hz, 1H, H_6), 6.93 (d, J = 1.9 Hz, 1H, H_4), 4.46 (s, 2H, $-CH_2-$), 4.39 (t, J = 7.0 Hz, 2H, CH_2), 3.84 (bs, 1H, OH), 3.60 (s, 3H, CH_3), 2.80 (t, J = 7.0 Hz, 2H, CH_2).^{13}C NMR ($CDCl_3$, 300 MHz), δ (ppm): 171.7,

160.0, 138.0, 130.8, 128.5, 98.3, 79.02, 52.3, 51.3, 47.8, 32.6. MS (70 eV) *m*/*z* (%): 236 (M^+, 8), 205 (2), 177 (2), 150 (44).

General Procedure for the Aza-Michael/Stille Sequence on A1−3 (Method E). A mixture of azinone **A** (1.0 mmol), the corresponding Michael acceptor (**B**) (1.0 mmol), and K_2CO_3 (1.2 mmol) in toluene (2.5 mL) was heated (80 °C) until the starting material (**A**) was consumed. After cooling, the corresponding stannane (**E**) (1.1 mmol) and $PdCl_2(PPh_3)_2$ (0.10 mmol) were added and heated (80 °C) for 3−8 h. The mixture was allowed to cool to room temperature, filtered through a Celite pad, and washed (AcOEt, 3 times), and the filtrate was evaporated to dryness to give an oily residue that was poured into water. After extraction with dichloromethane, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel) to obtain analytically pure samples.

3-(2-Oxo-5-thiophen-2-yl-2*H*-pyridin-1-yl)-propionitrile (A1B1E1). Purification by column chromatography using AcOEt/hexane (1:2) as eluent afforded a solid. Yield: 61%. IR (KBr): ν_{max}/cm^{-1} 2250 (C≡N), 1666 (CO), 1604 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.61 (d, J = 9.2 Hz, 1H, CH), 7.59 (m, 1H, CH), 7.58 (d, J = 2.1 Hz, 1H, CH), 7.22 (d, J = 0.9 Hz, 1H, CH), 7.20 (d, J = 0.9 Hz, 1H, CH), 7.05 (m, 2H, aromatics), 6.60 (d, J = 9.2 Hz, CH), 4.17 (t, J = 6.3 Hz, $-CH_2-$), 2.90 (t, J = 6.3 Hz, $-CH_2-$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 161.6, 140.2, 139.1, 134.0, 128.5, 125.0, 123.5, 121.5, 117.5, 115.6, 46.9, 17.6. MS (70 eV) *m*/*z* (%): 230 (M^+, 100), 177 (100), 162 (33).

3-(6-Oxo-4-vinyl-6*H*-pyridazin-1-yl)-propionic Acid Methyl Ester (A2B2E4). Purification by column chromatography using AcOEt/hexane (1:1) as eluent afforded a yellow oil. Yield: 69%. IR (KBr): ν_{max}/cm^{-1} 1730 (CO), 1662 (CO). ^1H NMR ($CDCl_3$, 75 MHz), δ (ppm): 7.83 (s, 1H, H_6), 6.67 (s, 1H, H_4), 6.45 (dd, J = 6.7 Hz, J = 10.9 Hz, 1H, CH), 5.89 (d, J = 17.7 Hz, 1H, CH), 5.55 (d, J = 10.9 Hz, 1H, CH), 4.36 (t, J = 7.1 Hz, 2H, CH_2), 3.62 (s, 3H, CH_3), 2.76 (t, J = 7.1 Hz, 2H, CH_2).^{13}C NMR ($CDCl_3$, 300 MHz), δ (ppm): 171.7, 160.8, 140.5, 134.7, 131.6, 125.0, 122.3, 52.2, 47.4, 32.8. MS (70 eV) *m*/*z* (%): 208 (M^+, 100), 176 (18), 149 (31), 215 (30).

3-(6-Oxo-3-phenyl-4-vinyl-6*H*-pyridazin-1-yl)-propionitrile (A3B1E4). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 68%. IR (KBr): ν_{max}/cm^{-1} 2248 (CN), 1654 (CO), 1570 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.46 (m, 5H, aromatics), 7.05 (s, 1H, H_4), 6.44 (dd, J = 6.3 Hz, J = 10.9 Hz, 1H, CH), 5.87 (d, J = 17.3 Hz, 1H, CH), 5.52 (d, J = 10.9 Hz, 1H, CH), 4.49 (t, J = 6.7 Hz, 2H, $-CH_2$), 2.94 (t, J = 6.7 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.4, 147.4, 142.7, 134.8, 132.2, 129.7, 129.5, 128.9, 124.8, 122.4, 117.4, 47.5, 17.0. MS (70 eV) *m*/*z* (%): 251 (M^+, 19), 250 (29), 197 (100), 141 (41).

3-(6-Oxo-3-phenyl-4-vinyl-6*H*-pyridazin-1-yl)-propionic Acid Methyl Ester (A3B2E4). Purified by column chromatography using AcOEt/hexane (1:2) as eluent. Yield 64%. IR (KBr): ν_{max}/cm^{-1} 1746 (CO), 1661 (CO), 1584 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.42 (m, 5H, aromatics), 7.02 (s, 1H, H_4), 6.44 (dd, J = 6.3 Hz, J = 10.9 Hz, 1H, CH), 5.84 (d, J = 17.3 Hz, 1H, CH), 5.48 (d, J = 10.9 Hz, 1H, CH), 4.50 (t, J = 7.1 Hz, 2H, $-CH_2$), 3.64 (s, 3H, CH_3), 2.86 (t, J = 7.1 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.8, 160.5, 146.5, 141.9, 135.2, 132.4, 129.4, 128.8, 124.7, 121.9, 52.2, 47.5, 33.0, 1.41. MS (70 eV) *m*/*z* (%): 284 (M^+, 24), 225 (18), 197 (100), 141 (16).

3-[4-(1-Ethoxyvinyl)-6-oxo-3-phenyl-6*H*-pyridazin-1-yl]-propionitrile (A3B1E5). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 62%. IR (KBr): ν_{max}/cm^{-1} 2249 (CN), 1730 (CO), 1665 (CO), 1590 (aromatics), 1088 (C−O−C). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.46 (m, 2H, aromatics), 7.38 (m, 3H, aromatics), 7.00 (s, 1H, H_4), 4.46 (t, J = 6.8 Hz, 2H, $-CH_2$), 4.43 (d, J = 2.7 Hz, 1H, −CH), 4.30 (d, J = 2.7 Hz, 1H, −CH), 3.52 (q, J = 6.9 Hz, 2H, CH_2), 2.85 (t, J = 6.8 Hz, 2H, $-CH_2$), 0.81 (t, J = 6.9 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.1, 157.3, 146.7, 142.6, 136.3, 129.1, 128.4, 128.4, 128.0, 117.4, 89.9, 54.4, 47.5, 17.0, 14.0. MS (70 eV) *m*/*z* (%): 295 (M^+, 2), 266 (20), 213 (100), 114 (24).

3-[4-(1-Ethoxyvinyl)-6-oxo-3-phenyl-6*H*-pyridazin-1-yl]-propionic Acid Methyl Ester (A3B2E5). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 67%. IR (KBr): ν_{max}/cm^{-1} 1734 (CO), 1670 (CO), 1590 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.47 (m, 2H, aromatics), 7.44 (m, 3H, aromatics), 6.97 (s, 1H, H_4), 4.49 (t, J = 7.2 Hz, 2H, $-CH_2$), 4.42 (d, J = 2.7 Hz, 1H, −CH), 4.29 (d, J = 2.7 Hz, 1H, −CH), 3.64 (s, 3H, CH_3), 3.51 (q, J = 6.9 Hz, 2H, CH_2), 2.85 (t, J = 7.2 Hz, 2H, $-CH_2$), 0.81 (t, J = 6.9 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.8, 160.2, 157.6, 145.8, 141.8, 136.7, 128.9, 128.4, 128.3, 128.0, 89.5, 64.3, 52.2, 47.5, 33.0, 14.0. MS (70 eV) *m*/*z* (%): 328 (M^+, 2), 299 (15), 267 (21), 213 (100), 128 (40), 115 (43).

3-[4-(1-Ethoxyvinyl)-6-oxo-3-phenyl-6*H*-pyridazin-1-yl]-propionic Acid Ethyl Ester (A3B3E5). Purification by column chromatography using AcOEt/hexane (1:4) as eluent afforded a solid. Yield 68%. IR (KBr): ν_{max}/cm^{-1} 1733 (CO), 1661 (CO), 1590 (aromatics), 1088 (C−O−C). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.45 (m, 2H, aromatics), 7.36 (m, 3H, aromatics), 6.98 (s, 1H, H_4), 4.49 (t, J = 7.2 Hz, 1H, −CH), 4.42 (d, J = 2.7 Hz, 2H, $-CH_2$), 4.29 (d, J = 2.7 Hz, 2H, $-CH_2$), 4.10 (q, J = 7.1 Hz, 2H, CH_2), 3.51 (q, J = 6.9 Hz, 2H, CH_2), 2.84 (t, J = 7.2 Hz, 2H, −CH2), 1.18 (t, J = 7.2 Hz, 2H, $-CH_2$), 0.81 (t, J = 6.9 Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.4, 160.3, 157.6, 145.8, 141.8, 136.7, 128.9, 128.4, 128.3, 128.0, 89.5, 64.3, 61.1, 47.5, 33.2, 14.4, 14.0. MS (70 eV) *m*/*z* (%): 342 (M^+, 2), 313 (7), 213 (100).

3-(6-Oxo-3-phenyl-4-thiophen-2-yl-6*H*-pyridazin-1-yl)-propionitrile (A3B1E1). Purification by column chromatography using AcOEt/hexane (1:2) as eluent afforded a solid. Yield 60%. IR (KBr): ν_{max}/cm^{-1} 2251 (CN), 1655 (CO), 1578 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.33 (m, 6H, aromatics + 1H, CH), 7.05 (s, 1H, H_4), 6.90 (dd, J = 3.8 Hz, J = 1.4 Hz, 1H, CH), 6.74 (d, J = 3.8 Hz,

1H, CH), 4.49 (t, $J = 6.9$ Hz, 2H, $-CH_2$), 2.95 (t, $J = 6.9$ Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 158.9, 146.0, 139.0, 136.0, 134.6, 129.4, 128.9, 128.7, 128.6, 128.0, 127.5, 126.8, 116.7, 47.0, 16.7. MS (70 eV) *m*/*z* (%): 307 (M^+, 60), 253 (79), 197 (100), 152 (29).

3-(6-Oxo-3-phenyl-4-thiophen-2-yl-6*H*-pyridazin-1-yl)-propionic Acid Methyl Ester (A3B2E1). Purification by column chromatography using AcOEt/hexane (1:4) as eluent afforded a solid. Yield 62%, mp 79−80 °C (*i*-PrOH). IR (KBr): ν_{max}/cm^{-1} 1734 (CO), 1656 (CO), 1590 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.31 (m, 5H, aromatics + 1H, thiophene), 7.02 (s, 1H, H_4), 6.87 (dd, $J =$ 3.8 Hz, $J = 1.4$ Hz, 1H, thiophene), 6.88 (d, $J = 3.8$ Hz, 1H, thiophene), 4.50 (t, $J = 7.1$ Hz, 2H, $-CH_2$), 3.64 (s, 3H, CH_3), 2.87 (t, $J = 7.1$ Hz, 2H, $-CH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.8, 159.9, 146.0, 139.0, 137.1, 135.7, 129.9, 129.6, 129.4, 129.0, 128.6, 128.1, 127.6, 52.2, 47.5, 33.0. MS (70 eV) *m*/*z* (%): 340 (M^+, 41), 253 (100), 197 (84).

General Procedure for the Aza-Michael/Alkylation/Stille Sequence on A4 (Method F). A mixture of azinone **A** (1.0 mmol), the corresponding Michael adduct (**B**) (1.0 mmol), and K_2CO_3 (1.1 mmol) in 3:1 MeCN/H_2O (2.5 mL) was stirred and heated (40 °C) until complete consumption of **A** (30−60 min). After cooling, the proper alkyl halide (**G**) (1.4 mmol) was added, and the mixture was heated at 70 °C for 0.5−1h. On cooling, diatomaceous earth was added to the solution, and the mixture was stirred at room temperature. Filtration and washing (MeCN, 2 times) yielded a clear solution that was treated with the corresponding stannane (**E**) (1.5 mmol) and $PdCl_2(PPh_3)_2$ (0.05 mmol). The mixture was heated (80 °C) for 4−8 h, then cooled to room temperature, diluted with dichloromethane, filtered through a Celite pad, and washed (AcOEt, 3 times). The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel) to obtain analytically pure samples.

3-(3-Ethoxycarbonylmethyl-2,4-dioxo-5-phenyl-3,4-dihydro-2*H*-pyrimidin-1-yl)-propionic Acid Ethyl Ester (A4B3G2E2). Purification by column chromatography using AcOEt/hexane (1:3) as eluent afforded a solid. Yield 40%, mp 116−117 °C (*i*-PrOH). IR (KBr): ν_{max}/cm^{-1} 1735 (CO), 1688 (CO), 1652 (CO), 1565 (aromatics), 1085 (C−O−C). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.55 (s, 1H, CH), 7.45 (m, 2H, aromatics), 7.34 (m, 3H, aromatics), 4.70 (s, 2H, CH_2), 4.18 (q, $J = 7.1$ Hz, 2H, CH_2), 4.01 (t, $J = 5.9$ Hz, 2H, $-CH_2$), 3.66 (s, 3H, CH_3), 2.78 (t, $J = 5.9$ Hz, 2H, $-CH_2$), 1.24 (t, $J = 7.1$ Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.7, 167.7, 161.4, 150.5, 141.6, 132.4, 128.3, 128.1, 127.8, 113.8, 61.4, 52.0, 46.1, 42.4, 42.2, 32.6, 14.0. MS (70 eV) *m*/*z* (%): 360 (M^+, 100), 287 (13), 227 (18), 172 (34), 130 (75), 102 (53), 59 (62).

3-(3-Ethyl-2,4-dioxo-5-phenylethynyl-3,4-dihydro-2*H*-pyrimidin-1-yl)-propionic Acid Ethyl Ester (A4B3G1E3). Purification by column chromatography using AcOEt/hexane (1:5) as eluent afforded a solid. Yield 33%. IR (KBr): ν_{max}/cm^{-1} 1728 (CO), 1706 (CO), 1656 (CO), 1123 (C−O−C). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.81 (s, 1H, CH), 7.50 (m, 2H, aromatics), 7.31 (m, 3H, aromatics), 4.15 (t, $J = 5.9$ Hz, 2H, $-CH_2$), 4.04 (q, $J = 7.1$ Hz, 2H, $-CH_2$), 4.02 (q, $J = 7.1$ Hz, 2H, $-CH_2$), 2.76 (t, $J = 5.9$ Hz, 2H, $-CH_2$), 1.26 (t, $J = 7.1$ Hz, 3H, $-CH_3$), 1.25 (t, $J = 7.1$ Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.5, 162.0, 150.3, 148.3, 146.1, 132.0, 128.8, 128.6, 100.0, 93.5, 85.2, 61.6, 46.9, 37.5, 33.4, 14.5, 13.1. MS (70 eV) *m*/*z* (%): 340 (M^+, 100), 196 (65), 142 (51), 114 (32).

General Procedure for the Aza-Michael/Alkylation/Suzuki Sequence on A4 (Method G). The corresponding Michael acceptor (**B**) (1.0 mmol), azinone (**A**) (1.0 mmol), and K_2CO_3 (3.0 mmol) in DME/H_2O (3:1, 3 mL) were stirred and heated (40 °C) until complete consumption of **A** (0.5−1 h). After cooling to room temperature, the corresponding alkyl halide (**G**) was added and heated (70 °C) for 2−3 h. On cooling, the proper boronic acid (**C**) (2.2 mmol) and $Pd(PPh_3)_4$ (0.016 mmol) were added. The mixture was heated (80 °C) for 8−12 h. The solution was filtered through a Celite pad and washed (DME, 3 times), and the filtrate was evaporated to dryness to give a residue that was then purified by column chromatography (silica gel) or crystallization to obtain analytically pure samples.

3-(3-Benzyl-2,4-dioxo-5-styryl-3,4-dihydro-2*H*-pyrimidin-1-yl)-propionic Acid Ethyl Ester (A4B2G3C5). Purification by column chromatography using AcOEt/hexane (1:5) as eluent afforded a solid. Yield 43%. IR (KBr): ν_{max}/cm^{-1} 1702 (CO), 1680 (CO), 1653 (CO), 1531 (aromatics). ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.53 (s, 1H, CH), 7.51 (m, 3H, aromatics), 7.35 (m, 8H, aromatics + CH), 6.84 (d, $J = 16.4$ Hz, 1H, −CH), 5.17 (s, 2H, $-CH_2-$), 4.13 (q, $J = 7.1$ Hz, 1H, CH_2), 4.04 (t, $J = 6.0$ Hz, 2H, $-CH_2$), 2.79 (t, $J = 6.0$ Hz, 2H, $-CH_2$), 1.24 (t, $J = 7.1$ Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 171.3, 161.9, 150.5, 140.0, 137.3, 136.6, 129.3, 129.0, 128.5, 128.4, 128.3, 127.6, 126.9, 126.3, 111.3, 61.1, 46.3, 44.6, 33.0, 14.0. MS (70 eV) *m*/*z* (%): 404 (M^+, 27), 170 (13), 115 (23), 91 (100).

General Procedure for the Aza-Michael/Alkylation/Heck Sequence on A4 (Method H). A mixture of **A4** (1.0 mmol), the corresponding Michael acceptor (**B**) (1.0 mmol), and K_2CO_3 (2.0 mmol) in a 3:1 MeCN/H_2O mixture (2.5 mL) was stirred and heated (40 °C) until the starting material (**A**) was consumed (4−7 h). After cooling, the alkyl halide (**G**) (1.5 mmol) was added and the mixture was heated (80 °C) for 0.5−1 h. On cooling, palladium catalyst (5 mol %, 10% Pd/C) and the corresponding olefin (1.5 mmol) were added. The mixture was heated (70 °C) until the complete disappearance of the intermediate (5−10 h) and then allowed to cool at room temperature. After cooling, the solvent was evaporated. For those reactions performed in the presence of water, the mixture was diluted with 2 mL of the other solvent (DME or CH_3CN) and stirred for 10 min with diatomaceous earth; filtered and washed; and the filtrate was evaporated to dryness. The residue was purified by column chromatography (silica gel) to obtain analytically pure samples.

3-[3-Ethyl-1-(2-methoxycarbonyl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-acrylic Acid Methyl Ester (A4B2G1B2). Purification by column chromatography using AcOEt/hexane (1:4) as eluent afforded a solid. Yield 45%,

mp 140−141 °C IR (KBr): ν_{max}/cm^{-1} 1714 (CO), 1689 (CO), 1659 (CO), 1108 (C−O−C). ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.64 (s, 1H, CH), 7.33 (d, J = 15.7 Hz, 1H, CH), 6.96 (d, J = 15.7 Hz, 1H, CH), 4.05 (t, J = 5.7 Hz, 2H, $-CH_2$), 4.01 (q, J = 6.9 Hz, 2H, $-CH_2$), 3.74 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 2.80 (t, J = 5.7 Hz, 2H, $-CH_2$), 1.21 (t, J = 6.9 Hz, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 172.1, 168.4, 161.2, 150.3, 146.0, 137.2, 118.9, 109.1, 52.7, 51.9, 46.9, 37.1, 33.0, 13.1. MS (70 eV) *m*/*z* (%): 310 (M^+, 2), 251 (100), 180 (15), 59 (13).

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Supporting Information Available. Copies of ^{1}H NMR, ^{13}C NMR, IR, and mass spectra for representative compounds and isolated intermediates are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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