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The Journal of Organic Chemistry 2020 85 (4), 2486-2503

DOI: 10.1021/acs.joc.9b03174

Intramolecular Palladium(II)-catalyzed 6-*endo* C-H alkenylation directed by the remote *N*-protecting group. Mechanistic insight and application to the synthesis of dihydroquinolines

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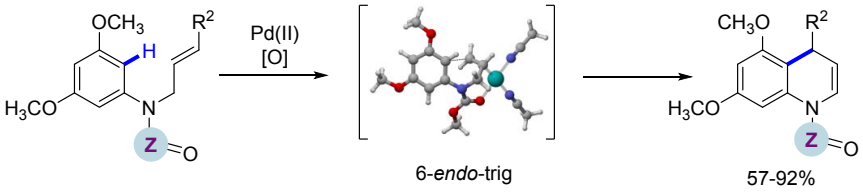


Abstract. A protocol for the Pd(II)-catalyzed C-H alkenylation reaction of substituted *N*-allylanilines *via* an unusual 6-*endo* process has been developed. A DFT study of the mechanistic pathway has shown that the coordination of the remote protecting group to the palladium center is determinant for the control of the regioselectivity in favor of the 6-*endo* process. The reaction would proceed *via* prior

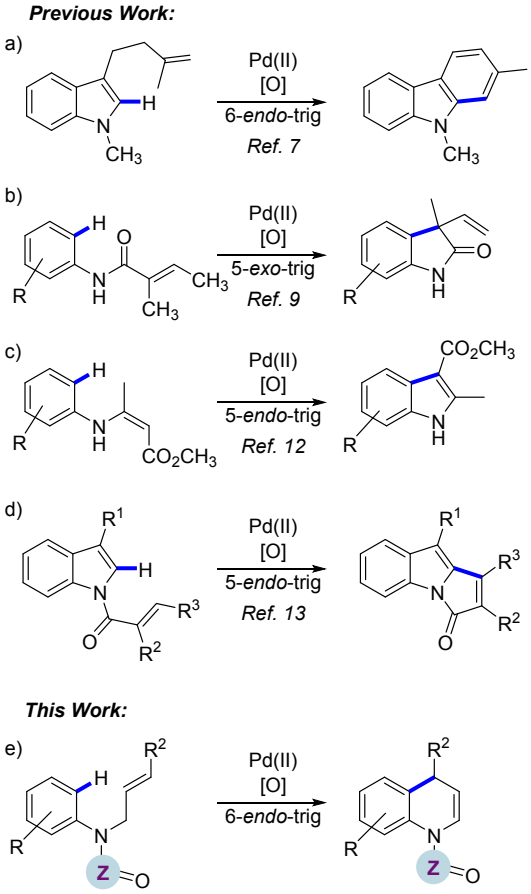
activation of the alkene. This procedure constitutes a mild and efficient method for the synthesis of 1,4-dihydroquinoline derivatives from simple and readily accessible substrates.

Introduction

Transition-metal catalyzed C-H functionalization reactions of (hetero)arenes have emerged as very powerful tools for the formation of carbon-carbon bonds,[1] and as a good alternative to traditional cross-coupling chemistry. No prefunctionalized coupling precursors, as halides or pseudohalides are required, though a stoichiometric oxidant is needed to regenerate the active catalytic species. These reactions can typically be carried out under mild conditions, even in aqueous media, avoiding the need for rigorous exclusion of oxygen. In the last years, there has been great progress in the intermolecular dehydrogenative Heck reaction (DHR) or Fujiwara –Moritani reaction.[2] This reaction consists of the Pd(II)–catalyzed direct coupling between a Csp^2-hybridized reaction partner and an alkene followed by β-hydride elimination towards the site of initial migratory insertion, which formally provides a sp^2–sp^2 carbon–carbon bond. The main issue of these type of reactions has been the control of site selectivity, that has been addressed by using either electronically activated substrates or directing groups/ligands are able to coordinate the metal center and facilitate the catalyst approach to the selected C-H.[3] The potential of its intramolecular variant for the synthesis of carbocyclic and heterocyclic frameworks, however, remains relatively underexplored, and has been mainly applied to electron-rich heteroarenes such as indole and pyrrole. As in related Heck cyclizations, the regioselectivity is determined by the ring size and the preferential *exo* processes, which has been attributed to the strain involved in the approach of the arylpalladium intermediate. Thus, annulated indoles and pyrroles have been prepared via 5-, 6- and/or 7-*exo*-trig cyclizations of C-3 and/or C-2 substituted derivatives with unactivated alkenes.[4] The procedure has also been applied to the construction of benzofurans and chromenes using electron-rich arenes.[5] Specifically, our group has reported intramolecular dehydrogenative Heck reactions of aryl homoallyl ethers and *N*-homoallylanilines, which provide direct access to highly and diversely substituted chromenes and (dihydro)quinolines, respectively.[6] On the other hand, *endo*-trig cyclizations

are rare and have been reported when the *exo* processes are blocked, and the palladium hydride elimination is not possible, as described by Lu in the synthesis of carbazoles[7] (Scheme 1a).

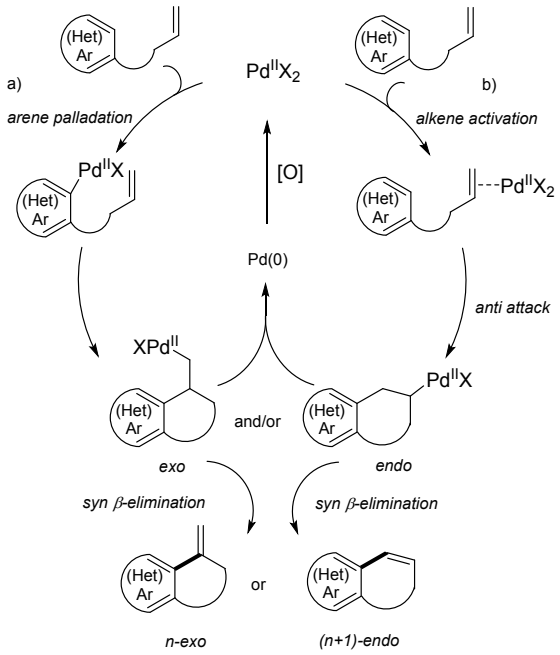
The palladium-catalyzed cyclization / carboalkoxylation of C-2 and C-3 alkenyl indoles to give carbazoles and cyclohepta[*b*]indoles *via* either 6 or 7-*exo*-trig, as well as 6-*endo*-trig processes is still an exception in dehydrogenative Heck-type cyclizations.[8] Similarly, *exo* cyclizations are generally favored using activated alkenes (bearing an EWG). Thus, Pd(II)-catalyzed intramolecular reactions of *N*-phenylacrylamides afford oxindoles *via* formal 5-*exo*-trig processes, (Scheme 1b),[9] and in some cases, even when β-hydride elimination is not possible, the Ar-Pd(II)-intermediate prefers to undergo a nucleophile capture or a subsequent C-H alkylation.[10] However, we have demonstrated that the intramolecular 6-*endo*-trig C–H alkenylation of related *N*-alkyl substituted *N*-phenylacrylamides gives 4-substituted quinolin-2[*1H*]-ones,[11] showing that the reaction can be switched to the β-position of the acrylamide by selecting the catalyst, oxidant, and experimental conditions. On the other hand, Glorius[12] has achieved the synthesis of indoles by a formal Pd(II)-catalyzed oxidative 5-*endo* cyclization of substituted *N*-arylenamine carboxylates, although, as in the work of Oestreich,[9] a free NH is required for the success of the reaction (Scheme 1c). The size of the formed ring can also be decisive for the regioselectivity, as in the cyclization of 1-(1*H*-indol-1-yl)prop-2-enone derivatives to give 3*H*-pyrrolo[1,2-*a*]indol-3-ones that takes place *via* a 5-*endo*-trig cyclization[13] (Scheme 1d).



Scheme 1. Intramolecular Pd(II)-catalyzed alkenylation reactions through *endo* and *exo* processes.

Two alternative mechanistic pathways have been generally proposed for the initial palladation that would be determinant for the *endo*/*exo* selectivity (Scheme 2). The reaction could proceed through an arene metalation-alkene insertion (Scheme 2a) or alkene activation-arene insertion (Scheme 2b). Both reaction pathways have been proposed to explain *endo* and *exo* insertions, in some cases without providing experimental or theoretical evidences in favor of any of them. However, both pathways differ in the stereochemical outcome and may lead to the formation of different diastereomers using the appropriate substrate: in pathway a), the (hetero)aryl palladium(II) intermediate would undergo a *syn* olefin insertion, followed by *syn* β-hydride elimination. On the other hand, *anti* nucleophilic attack of the arene to the Pd(II) complex would take place on an Pd(II)-coordinated alkene (pathway b) In both cases, reductive elimination generates the reaction product and a Pd(0) complex that can be reoxidized to Pd(II). Thus, there is stereochemical support for a mechanism involving initial palladation of the (hetero)arene[4a,5a,c] or attack of the heteroarene to the palladium-complexed olefin.[8,14] This Friedel-Crafts

type mechanism has also been proposed for the obtention of oxyndoles (Scheme 1b),[9] but also, depending on the substrate used, different mechanismsm have been propsed, such as the electrophilic palladation of an electron rich enamine, followed by deprotonation of the aromatic ring (Scheme 1c).[12] Hence, a mechanistic understanding of the reaction is required in order to obtain selectively the desired reaction products. In the context of our interest in this type of cyclization reactions[6,11] we decided to study the Pd(II)-catalyzed intramolecular alkenylation of *N*-protected allyl anilines to obtain dihydroquinolines (DHQ) through a 6-*endo* process (Scheme 1d).



Scheme 2. Schematic mechanistic pathways for the intramolecular Pd(II)-catalyzed alkenylation reactions.

Partially hydrogenated quinolines are important structural frameworks present in a myriad of bioactive natural products and pharmaceuticals, as well as building blocks in organic synthesis.[15] Among them 1,4-dihydroquinolines (1,4-DHQ) have attracted special attention, due to their important biological activities. For example, 4-aryl-1,4-dihydroquinoline derivatives have been characterized as a novel class of ABCB1 inhibitors to reverse the multidrug resistance of anticancer drugs.[16] Besides, 1,4-dihydroquinoline is the core of the azapodophyllotoxins, known antiproliferative microtubule destabilizing agents that have expressed very pronounced antitumor activity.[17] 1,4-DHQ can also be

used as drug carriers for specific delivery to the CNS in the treatment of Alzheimer's disease[18] or cerebral ischemia/reperfusion injury,[19] as well as in the targeting of PET radioligands for brain imaging.[20] On the other hand, they are used as building blocks in the synthesis[21] of pyridoacridones, a family of marine alkaloids that exhibits an array of biological activities (Figure 1).[22] Therefore, the synthesis of substituted 1,4-dihydroquinolines is interesting in both synthetic and medicinal chemistry.

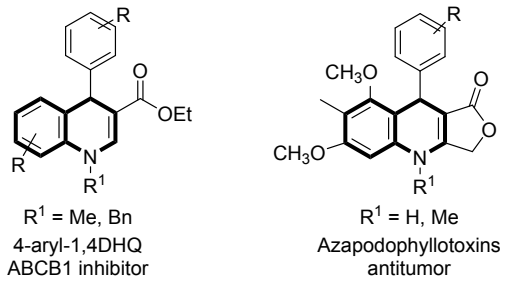
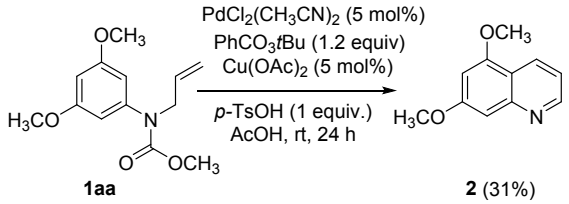


Figure 1. Selected biologically active 1,4-dihydroquinolines

Although many examples of the catalytic synthesis of quinolines and tetrahydroquinolines have been reported,[23] there have been relatively few examples of the preparation of 1,4-dihydroquinoline derivatives. Herein we report a joint experimental and DFT study on the 6-*endo* cyclization on *N*-protected allyl anilines that has led to an efficient method for the synthesis of 1,4-dihydroquinoline derivatives from simple and readily accessible substrates. The protecting group on nitrogen atom has been shown to be crucial to favor the *endo* cyclization process.

Results and Discussion

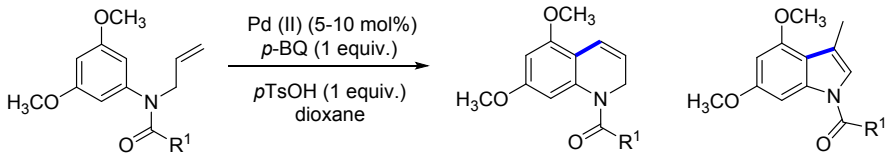
We selected carbamate **1aa** as a model substrate (Scheme 3), using as starting point the reaction conditions that had been previously optimized for the 6-*endo* cyclization of *N*-aryl acrylamides to quinolones.[11] Under these conditions, quinoline **2** was obtained, although in a low yield (31%), together with decomposition products. Quinoline **2** would be obtained from a 6-*endo* cyclization followed by deprotection under the strongly acidic conditions, and further oxidation.



Scheme 3. Cyclization of **1aa**

Consequently, to avoid the deprotection and additional oxidation, we switched to milder reaction conditions, using dioxane as solvent and *p*-benzoquinone as the only oxidant (Table 1). The use of *p*-toluensulfonic acid is also important to enhance the reactivity probably through the formation of a more electrophilic Pd(II) species.[6] Under these conditions, the 6-*endo* cyclization took place with complete regioselectivity, obtaining 1,2-dihydroquinoline **3aa** in high isolated yield (85%) after 16 h at room temperature (Table 1, entry 1). Formation of indole **4aa**, through a 5-*exo* process was not detected. Interestingly, when the protecting group is changed to a *t*-butyl carbamate (**1ba**, Table 1, entry 2), under the same reaction conditions the reaction was sluggish, obtaining **3ba** in much lower yield (38%), along with trace amounts of the 5-*exo* cyclization product **4ba** (not isolated) and decomposition products. An increase in the catalyst loading to a 10 mol% (Table 1, entry 3) resulted in a faster reaction (1.5 h at room temperature). However, although the dihydroquinoline **3ba** was obtained in higher yield (58%), the reaction was not selective, isolating a significant amount of indole **4ba**, through a 5-*exo* process. The change of the palladium precatalyst (Table 1, entry 4) gave a similar result. The use of a monoprotected aminoacid[24] (Boc-Val-OH) in this case did not accelerate the reaction rate, and led also to a non selective reaction (entry 5), also when the palladium source was changed trying to obtain more electrophilic palladium intermediates (Table 1, entries 6 and 7). The use of benzyl carbamate **1ca** led also to the regioselective formation of **3ca** (Table 1, entry 8). A significant difference in reactivity was observed when the nitrogen is protected as an amide: acetyl protected **1da** (Table 1, entry 9), did not react at all under the conditions used for **1aa** (Table 1, entry 1). It was necessary to increase the catalyst loading and to heat the reaction to 70 ºC to obtain full conversion (Table 1, entry 10). Although the 6-*endo* cyclization was the major reaction pathway obtaining a good yield of **3da**, indole **4da** was also isolated from the reaction mixture. Thus, the protecting group used has a strong influence in both the reactivity and the regioselectivity of the reaction, obtaining the best results with the methyl carbamate.

Table 1. Optimization of reaction conditions: protecting group



1 **3aa-3da** **4ba,da**

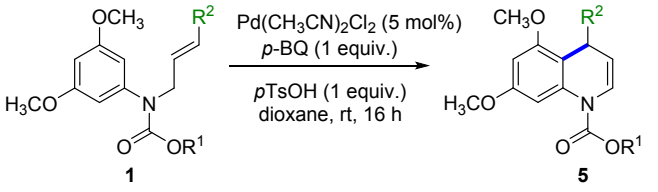
entry	**1**	R^1	[Pd(II)] (mol%)	t (h)	**3**	Yield (%)[a]	**4**	Yield (%)[a]
1	**1aa**	OCH_3	$Pd(CH_3CN)_2Cl_2$ (5)	16[b]	**3aa**	85	-	
2	**1ba**	O*t*Bu	$Pd(CH_3CN)_2Cl_2$ (5)	16[b]	**3ba**,	38	-	
3	**1ba**	O*t*Bu	$Pd(CH_3CN)_2Cl_2$ (10)	1.5[b]	**3ba**	58	**4ba**	16
4	**1ba**	O*t*Bu	$Pd(PhCN)_2Cl_2$ (10)	1.5[b]	**3ba**	56	**4ba**	13
5	**1ba**	O*t*Bu	$Pd(PhCN)_2Cl_2$ (10)[c]	2[b]	**3ba**	59	**4ba**	15
6	**1ba**	O*t*Bu	$Pd(PhCN)_2(BF_4)_2$ (10)[c]	3[b]	**3ba**	16[e]	**4ba**	3[e]
7	**1ba**	O*t*Bu	$Pd(OAc)_2$ (10)[c]	6[b]	**3ba**	21[f]	**4ba**	14[f]
8	**1ca**	OBn	$Pd(CH_3CN)_2Cl_2$ (10)	3[b]	**3ca**	67	-	
9	**1da**	CH_3	$Pd(CH_3CN)_2Cl_2$ (5)	20[b]	-[d]		-	
10	**1da**	CH_3	$Pd(CH_3CN)_2Cl_2$ (10)	1[g]	**3da**	85	**4da**	10

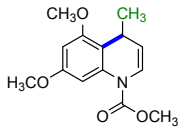
[a] Yield (%) of isolated pure compound. [b] room temperature. [c] Boc-Val-OH (20 mol%) was used as ligand. [d] no reaction. [e] Yield determined by ^{1}H NMR using DMAP as internal standard (55% conversion). [f] Yield determined by ^{1}H NMR using DMAP as internal standard (51% conversion). [g] 70 ºC.

Next, we extended the reaction to substrates bearing substituents on the alkene (**1ab-al**, Table 2). In all cases an electron rich aromatic ring was used, as we have previously shown in related reactions that it is required to obtain good reactivity.[6] It is noteworthy that in the all cases, the corresponding 1,4-dihydroquinolines **5** were obtained with complete regioselectivity. No formation of the indoles, or the corresponding 1,2-dihydroquinolines, was detected by NMR. Thus, 2-butenylaniline **1ab** (R^1 = R^2 = CH_3) gave only a moderate yield of **5ab** (Table 2, 57%), also in the presence of Boc-Val-OH. However,

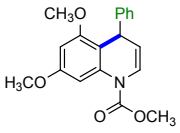
the reaction is best suited for the synthesis of 4-aryl substituted dihydroquinolines obtaining **5ac-5al** with high yields and complete regioselectivity under the standard conditions (Table 2).

Table 2. Synthesis of 4-substituted dihydroquinolines **5**.[a]

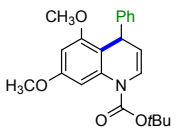




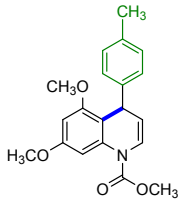
5ab 57%
56%[b,c]



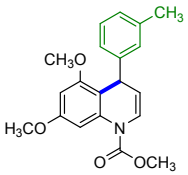
5ac 77%
79%[c]
89%[b,c]
85%[b,c,d]



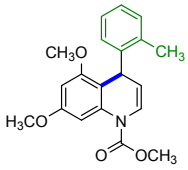
5bc 73%
86%[b,c]



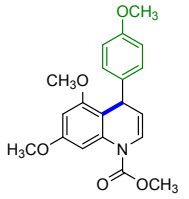
5ad 82%



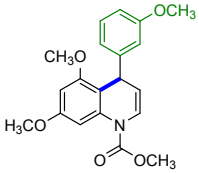
5ae 92%



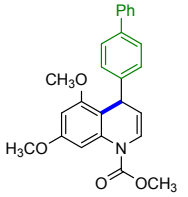
5af 82%



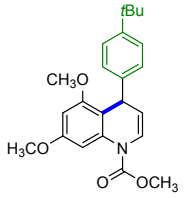
5ag 82%



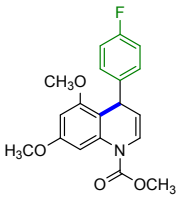
5ah 81%



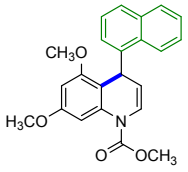
5ai 73%



5aj 87%



5ak 72%
85%[b,c]



5al 82%

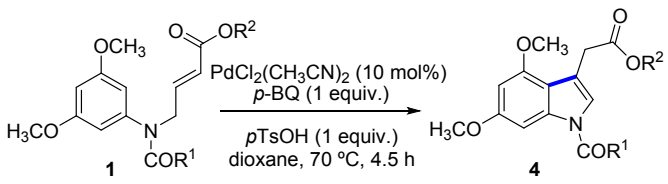
[a]Yield (%) of isolated pure product by column chromatography. [b] Boc-Val-OH (10 mol%) was used as ligand. [c] $Pd(PhCN)_2Cl_2$ (5 mol%) was used as catalyst.[d] 1 mmol scale.

The use of $Pd(PhCN)_2Cl_2$ in the reaction of **1ac** gave **5ac** in a similar yield (79%). However, the use of Boc-Val-OH as ligand improved significantly the yield (**5ac**, **5bc**, **5ak**). The yield of **5ac** was

comparable when the reaction was carried out in a 1 mmol scale (85 vs 89% yield). In this case, the use of the *t*-butyl carbamate as protecting group (**1bc**) did not imply a loss of selectivity, as **5bc** was obtained in similar yield, not detecting the formation of the indole in any case.

The regioselectivity of the reaction completely changed when electron withdrawing groups were introduced in the terminal position of the alkene (Table 3). Under the standard conditions, no reaction was observed for **1am**, and in this case, an increase of the catalyst loading to 10 mol% and heating to 70 ºC was required. Under these conditions indole **4am** was selectively obtained in a moderate yield (Table 3, entry 1). The same result was obtained with the Boc-protected substrate **1bm**, although indole **4bm** was isolated with lower yield (Table 3, entry 2), observing decomposition of the substrate. The reaction could be extended to different esters **1an-1aq**, obtaining selectively the indoles **4** with moderate to good yields (Table 3, entries 3-6). .

Table 3. Use electron deficient alkenes. Synthesis of indoles **4**

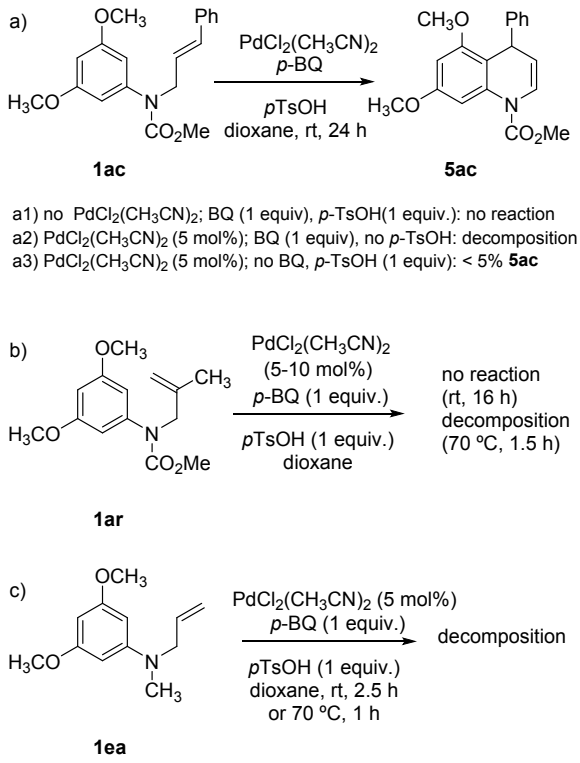


entry	**1**	R^1	R^2	**4**	Yield (%)[a]
1	**1am**	OCH_3	CH_3	**4am**	68
2	**1bm**	O*t*Bu	CH_3	**4bm**	41
3	**1an**	OCH_3	Et	**4an**	68
4	**1ao**	OCH_3	*n*Bu	**4ao**	63
5	**1ap**	OCH_3	*t*Bu	**4ap**	54
6	**1aq**	OCH_3	Bn	**4aq**	78

[a]Yield (%) of isolated pure product.

The results obtained show that the regioselectivity of the reaction is strongly influenced on one side by the protecting group on the nitrogen, and on the other side, by the nature of the alkene, leading to 6-

endo or 5-*exo* pathways. At this point, additional experiments were carried out in order to establish the scope and limitations of the reaction, and provide additional information on the possible reaction pathway. First, control experiments were carried out with **1ac** (Scheme 4a). In the absence of palladium, the reaction does not take place and unreacted **1ac** is recovered after 24 h at rt. When the reaction was carried out in the absence of *p*-TsOH, decomposition products were obtained. Finally, just a minor amount of **5ac** (<5%) was observed by ^{1}H NMR when the reaction was performed with no oxidant. The reaction is not compatible with substitution on the internal position of the alkene. Under standard conditions, **1ar** was unreactive, whereas only decomposition products were obtained when the reaction was heated at 70 ºC (Scheme 4b). The influence of the protecting group on nitrogen is clear, as only decomposition products were obtained when *N*-methyl aniline **1ea** is treated under the standard reaction conditions at rt or at 70 ºC. (Scheme 4c).

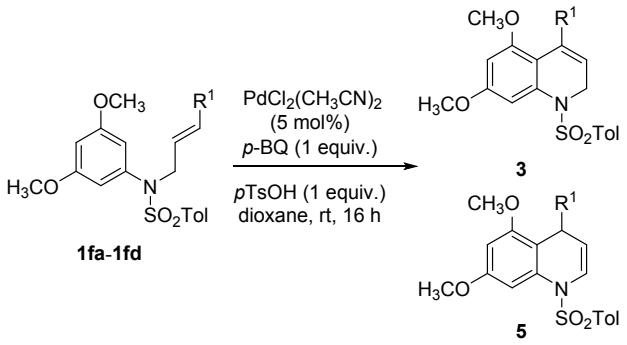


Scheme 4. Additional experiments

In view of these results, we next studied the effect of a *p*-toluensulfonyl group under the reaction conditions. Recently, *N*-allyl-arylsulfonamides have been used as precursors of tetrahydroquinolines in

a palladium catalyzed cascade reaction with benzenesulfonyl chlorides.[25] The proposed mechanism involves the initial coordination of the alkene to an arylpalladium(II) intermediate formed by oxidative addition of the sulfonyl chloride to Pd(0). Although the reaction results in a formal 6-*endo* cyclization, the proposed mechanistic pathway does not involve the cyclization of a substituted alkene. Under our reaction conditions, sulfonamide **1fa** gave 1,2-dihydroquinoline **3fa** with complete regioselectivity in an excellent yield (Table 4, entry 1), comparable to that obtained with carbamate **1aa** (Table 1, entry 1). However, **1fb** afforded a regioisomeric mixture of 1,2- and 1,4-dihydroisoquinolines **3fb** and **5fb** (Table 4, entry 2). In addition, **5fc** and **5fd** were selectively obtained, although with moderate yields (Table 4, entries 3 and 4).

Table 4. Use of *N*-tosyl-protected anilines **1f**

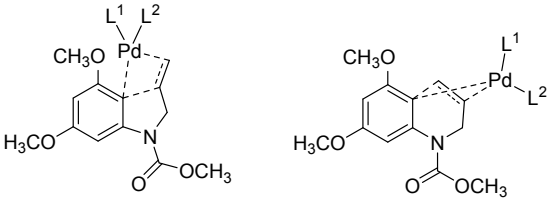


entry	**1**	R^1	**3**	Yield (%)[a]	**5**	Yield (%)[a]
1	**1fa**	H	**3fa**	87	**5fa**	-
2	**1fb**	CH_3	**3fb**	64	**5fb**	26
3	**1fc**	Ph	**3fc**	-	**5fc**	42
4	**1fd**	Bn	**3fd**	-	**5fd**	60

[a]Yield (%) of isolated pure product.

At this point, we decided to examine this reactivity pattern computationally, to get a more precise insight on the mechanistic course of the reaction. Substrate **1aa** was considered a useful starting point

for DFT calculations,[26] to explore the main role of the palladium catalyst in the mechanism (alkene activation or arene palladation, Scheme 2), and the subsequent 5-*exo*/6-*endo* selectivity of the cyclization process. Three key features of the reaction ought to be explained during the study, namely, the unusual 6-*endo* selectivity, the large influence of the *N*-protecting group on the reaction outcome, and the preference for 1,2- or 1,4-dihydroquinoline final product depending on the nature of the substituent at the alkene terminus. According to Scheme 2a, a hypothetical arene palladation would be followed by a *syn* insertion of the alkene into the Ar-Pd bond, which could occur through 5-*exo* or 6-*endo* pathways. Interestingly, the DFT computed activation barriers for palladium complexes of very diverse electronic properties show a general high preference for 5-*exo* insertion (Figure 2) in disagreement with the experimental results.



	L1	L2	ΔG‡(6-*endo*) − ΔG‡(5-*exo*)
TS1	OAc	OAc	10.7
TS2	OAc	none	6.7
TS3	MeCN	MeCN	6.1
TS4	MeCN	none	5.9
TS5	none	none	3.4

Figure 2. Computed activation energies for the alkene insertion into the Ar-Pd bond with complexes of different electronic properties

While this phenomenon presents no exception, more electron rich complexes like the anionic Pd(II) species in **TS1** show the largest *exo*/*endo* energy difference ($\Delta\Delta G^{\ddagger}$ = 10.7 kcal/mol). Decreasing the electronic charge in the metal center reduces consistently the *exo* preference (note the trend from **TS1** to **TS5** in Figure 2), but even the dicationic Pd complex in **TS5**, which lacks L1 and L2, is still not able to explain the formation of the quinoline moiety ($\Delta\Delta G^{\ddagger}$ = 3.4 kcal/mol). Thus, these data served to clearly

discard a mechanism involving cyclization after a previous arene palladation step, as hypothesized in Scheme 2a.

Meanwhile, low activation barriers were measured when the palladium complexes are activating the alkene towards a S_EAr cyclization step (Scheme 2b). However, once again, the major product of the reaction was predicted to be the 5-*exo* derivative, by a difference of 0.8 kcal/mol when an acetate is coordinated to the metal centre (**TS6**, Figure 3) and 2.2 kcal/mol for the chloride derivative. Noteworthy, if the coordination of the oxygen of the carbamate to the palladium centre is considered (Figure 4),[27] the interesting effect of a complete inversion of the *endo*/*exo* selectivity is observed. In all cases, the quinoline adduct becomes the preferred adduct **(TS8-TS11**), as experimentally noted. If a chloride is still coordinated to palladium, as in **TS8**, the activation energies are high, over 28 kcal/mol. The replacement of the chloride by a second molecule of MeCN reduces the values below 20 kcal/mol, predicting a feasible reaction in the experimental conditions. The *endo* regioselectivity is general for terminal (**TS9**) and substituted alkenes (**TS10** and **TS11**), and the energy difference with respect to the 5-*exo* counterparts is always high (3.0-10.0 kcal/mol), ensuring a complete regioselectivity. Even more, the tosylamide group can play a similar role, and the activation energies for the 6-*endo* approach are in the three cases (**TS12-TS14**) largely lower than those of the 5-*exo* transition states. The sense of regioselectivity seems logical, since the coordination of the carbamate to palladium induces a larger ring strain in the *exo* structures. On the other hand, the participation of the carbamate in the reaction through intramolecular coordination to the metal can help explaining the effect of the different substituents of nitrogen (Table 1). For example, increasing the steric bulkiness of the carbamate (O*t*Bu, Table 1, entries 2-8) or replacing the carbamate by an amide (Table 1, entries 9-10) can reduce their coordination ability, affecting negatively the reactivity and/or selectivity of the process.

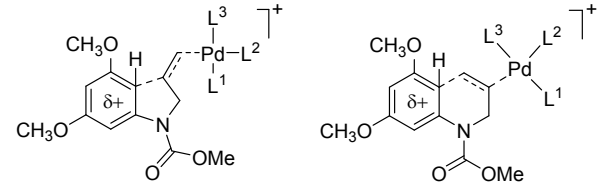


Figure 3. Predicted *endo*/*exo* selectivity of the S_EAr to the Pd(II) activated alkene

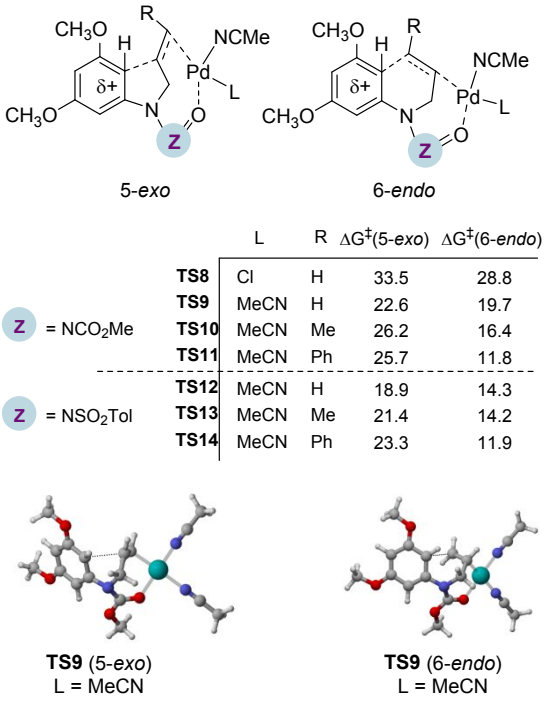
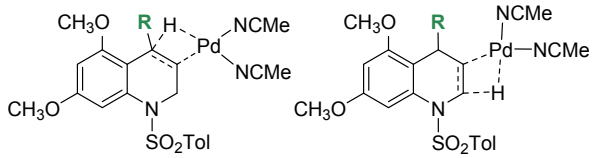


Figure 4. Computed activation energies for the cyclization after alkene activation by the Pd complexes.

The formation of different amounts of 1,2- or 1,4-dihydroquinoline products depending on the substitution at the alkene terminus is difficult to rationalize at the first sight. Thus, we calculated the β-elimination of the H atoms at the 2 or 4 positions of the cyclized palladium complexes, to ascertain whether the adduct formation is under kinetic or thermodynamic control. Interestingly, the calculations show that the 1,2-dihydro adduct **3** is slightly (*ca.* 1 kcal/mol) more stable than **5** regardless the R substituent (hydrogen, methyl, phenyl) present in the benzylic position, in complete disagreement with the results in Table 4. Thus, the regioselectivity is not dictated by the relative stability of adducts **3** and **5**. Gratifyingly, during the study of the kinetic conditions, the substrate bearing a terminal alkene (R=H,

TS15, Figure 5) was predicted to be deprotonated preferentially ($\Delta\Delta G^{\ddagger}$ = 2.4 kcal/mol) at the benzylic position to afford the 1,2-dihydro adduct, as in the experimental result (entry 1, Table 4). The conjugation of the forming double bond is probably responsible for this behavior. On the other hand, with phenyl as substituent (**TS17**), the computed and experimental selectivities also match, favoring the major 1,4-dihydro product. The steric hindrance between MeO/Ph and Ph/Pd moieties probably induces a severe increase in the activation barrier of the 1,2-dihydro transition state. The methyl group shows a mixed behavior; while **TS16** is energetically in between the two other cases, the reaction is experimentally non-selective (entry 2, Table 4). Nonetheless, the calculations are not able to predict correctly the right sense of selectivity for the methyl case, probably due to its borderline character.

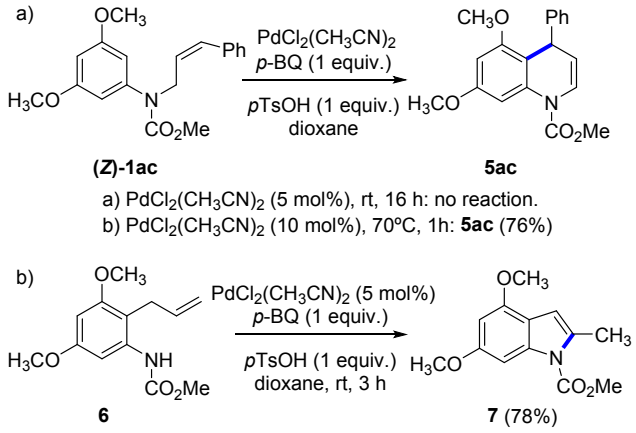


	$\Delta G^{\ddagger}$(1,4) - $\Delta G^{\ddagger}$(1,2)
TS15, R = H	+ 2.4
TS16, R = CH_3	- 2.1
TS17, R = Ph	- 4.5

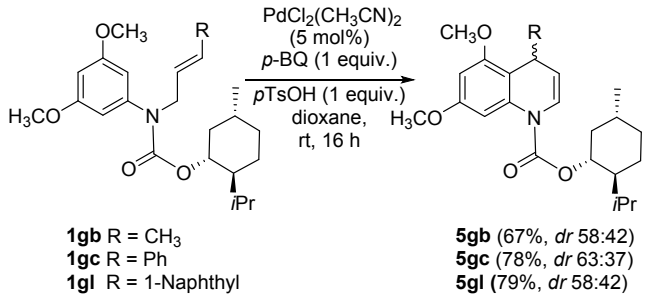
Figure 5. Computed activation energies for the β-elimination step, and comparison of the 1,2- and 1,4-dihydro pathways

Along these lines, we also found that the reaction is not stereospecific, and the 1,4-dihydroquinoline is formed, regardless of the geometry of the double bond in the starting material. Thus, (*Z*)-**1ac** required heating at 70º C and 10 mol% of catalyst to react, but yielded 1,4-dihydroquinoline **5ac** with good yield, not detecting the formation of the 1,2-dihydroquinoline (Scheme 5a). A mechanism involving a palladium catalyzed Claisen rearrangement followed by a 5-*exo* oxidative cyclization has been proposed for the obtainment of benzofurans from allyl aryl ethers.[5b] To rule out a related mechanism for the formation of the dihydroquinolines, the Claisen transposition product of **1aa** (*o*-allylaniline **6**) was prepared. Under the standard reaction conditions, the aza-Wacker reaction took place efficiently in only 3 h at rt, but exclusively through a 5-*exo* pathway, leading to 2-methylindole **7** in high yield (Scheme

5b). Finally, we studied the cyclization reaction using a chiral non-racemic carbamate as protecting group on the nitrogen. For this purpose, we selected the carbamate derived from (–)-menthol as protecting group. We reasoned that the coordination of the carbonyl with palladium in transition states such as those depicted in Figure 4 could favor a closer disposition of the auxiliary to the stereocenter being formed, and thus some extent of diastereoselectivity could be obtained that would not be expected without the coordination effect. As shown on Scheme 6, the reaction took place in good yield, and with modest, but appreciable, diastereoselectivity in the case of **5gc.**[28] Thus, the possibility of a modest 1,7-induction supports the coordination of the remote protecting group with palladium in the transition state leading to the C-C bond formation.



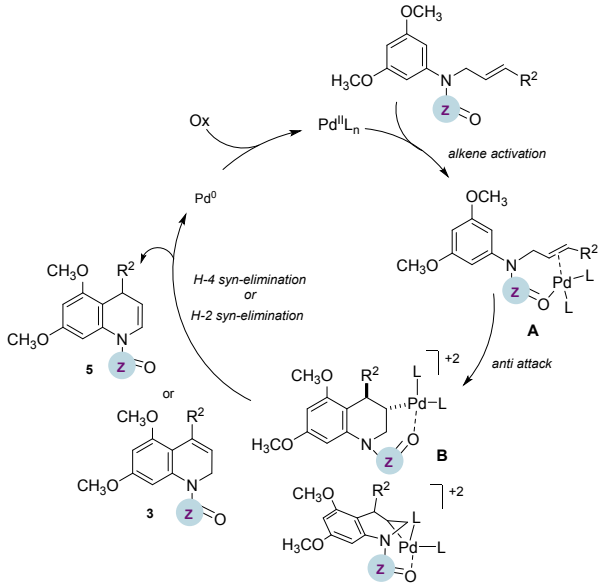
Scheme 5. Additional experiments



Scheme 6. Cylization of carbamates **1g**.

To sum up, a reaction pathway proposal in accordance with the computational and experimental data is shown in Scheme 7. Thus, the cyclization reaction would involve attack of the electron-rich aromatic ring onto the palladium-complexed olefin of **A**. As discussed earlier (see Figures 3 and 4), the formation

of intermediate **B** through a 6-*endo* process would be energetically favored by the effect of the coordination of palladium to the oxygen atom of protecting group on nitrogen. Finally, *syn* β-hydride elimination of H-2 or H-4 would account for the formation of 1,2-dihydro- or 1,4-dihydroquinolines **3** or **5** respectively. The formation of the more stable 1,2-dihydroquinoline is favored when R^2 = H, whereas H-4 elimination is preferential when R^2 = Ar (Figure 5).



Scheme 7. Mechanistic proposal.

In conclusion, an efficient procedure for the synthesis of 4-substituted 1,4-dihydroquinolines via Pd(II)-catalyzed 6-*endo* intramolecular C-H alkenylation reaction of readily accessible *N*-allylanilines has been developed. The regioselectivity is controlled by the nature of the protecting group on the nitrogen atom. DFT studies have provided understanding of the factors that govern this unusual 6-*endo* process, in agreement with the observed outcome of these cyclizations. The reaction proceeds via prior activation of the alkene, being the coordination of the remote protecting group to the palladium center crucial to favor the formation of the six-membered ring

Experimental Section

General experimental methods. Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained using an ATR. NMR spectra were recorded at 20-25 ˚C, at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C in $CDCl_3$ solutions. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Mass spectra were recorded under electron impact (EI) at 70 eV, chemical ionization (CI) at 230 eV, or with an ESI^+ source. Exact mass was obtained using a TOF detector. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography was performed on silica gel (230-400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 ˚C) and purged with argon. Heating blocks with temperature control were used, when necessary, for the reactions that required heating. Palladium catalysts were commercially available, and were used without further purification: $PdCl_2(CH_3CN)_2$ (99% purity), $Pd(OAc)_2$ (98%) and $Pd(CHCN)_4(BF_4)_2$ (99.9%).

Computational methods. All structures were optimized using density functional theory (DFT) as implemented in Gaussian with B3LYP as functional, 6-31G** as basis set for non-metallic atoms, and LANL2DZ as basis set for palladium. Final energies were obtained performing single-point calculations on the previously optimized structures using the M06 functional, 6-311+G** as basis set for non-metallic atoms and SDD for palladium. Solvation factors were introduced with the IEF-PCM method, using 1,4-dioxane as solvent. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies.

Synthesis of substituted *N*-allylanilines 1. Substrates **1** were prepared following the synthetic schemes described in the Supporting Information (Schemes S1, S2 and S3).

Alkylation reactions. Synthesis of substituted *N*-allylanilines 1a,b,c,g. General procedure (Scheme S1 a and c). Over a solution of the corresponding *N*-protected 3,5-dimethoxyaniline (1 mmol) in dry DMF (15 mL) at 0 ºC under argon atmosphere, NaH (60 % in mineral oil) (1.1 mmol) was added. The reaction was stirred at 0 ºC for 1 h, and afterwards, the corresponding allyl chloride (1.2 mmol) was

added. Then, the reaction was allowed to warm up to room temperature and stirred for 3-7.5 h. Afterwards, water (20 mL) was added and the aqueous layer was extracted with AcOEt (3 × 15 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/AcOEt) afforded the corresponding *N*-substituted *N*-allyl-3,5-dimethoxyanilines **1aa-1gc**.

Methyl allyl(3,5-dimethoxyphenyl)carbamate (1aa). Prepared from methyl (3,5-dimethoxyphenyl)carbamate (0.64 g, 3.03 mmol), NaH (60% in mineral oil) (0.13 g, 3.33 mmol) and allyl chloride (0.30 mL, 3.64 mmol). The reaction mixture was stirred at room temperature for 3 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 7/3) **1aa** was obtained as an oil (0.69 g, 91 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.69 (s, 6H), 4.15-4.21 (m, 2H), 5.05- 5.17 (m, 2H), 5.86 (ddt, J = 17.0, 10.2, 5.8 Hz, 1H), 6.30 (t, J = 2.2 Hz, 1H), 6.36 (d, J = 2.2 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 52.7, 53.2, 55.2, 98.5, 106.1, 116.9, 133.9, 143.7, 155.6, 160.7 ppm; IR (ATR): 1702 cm^{-1}; MS (EI) *m/z* (rel intensity): 251.1 (M^+, 93), 236.1 (100); HRMS (CI-TOF): calcd. for $C_{13}H_{18}NO_4$: 252.1236 [MH^+]; found, 252.1234.

***(E)*-Methyl-but-2-en-1-yl(3,5-dimethoxyphenyl)carbamate (1ab).** Prepared from methyl (3,5-dimethoxyphenyl)carbamate (0.46 g, 2.20 mmol), NaH (60% in mineral oil) (96.7 mg, 2.42 mmol) and (*E*)-1-chlorobut-2-ene (0.26 mL, 2.64 mmol). The reaction mixture was stirred at room temperature for 7 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 8/2) **1ab** was obtained as an oil and as a mixture of rotamers in a 75:25 ratio (0.51 g, 88 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (d, J = 6.0 Hz, 3H, minor rotamer), 1.64-1.68 (m, 3H, major rotamer), 3.69 (s, 3H, both rotamers), 3.76 (s, 6H, both rotamers), 4.07-4.22 (m, 2H, major rotamer), 4.27 (d, J = 6.3 Hz, minor rotamer), 5.53-5.62 (m, 2H, both rotamers), 6.33-6.40 (m, 3H, both rotamers) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 12.8 (minor rotamer), 17.7 (major rotamer), 47.2 (minor rotamer), 52.6 (major rotamer), 52.8 (both rotamers), 55.3 (both rotamers), 98.6 (major rotamer), 98.7 (minor rotamer), 106.4 (both rotamers), 126.1 (minor rotamer), 126.5 (major rotamer), 127.1 (minor rotamer), 128.6 (major rotamer), 143.8 (both rotamers), 155.7 (major rotamer), 155.8 (minor rotamer), 160.7 (minor rotamer),

160.8 (major rotamer) ppm; IR (ATR): 1702 cm^{-1} ; MS (EI) *m/z* (rel intensity): 265.2 (M^+, 49), 236.1 (100); HRMS (ESI-TOF): calcd. for $C_{14}H_{20}NO_4$: 266.1392 [MH^+]; found, 266.1403

Methyl cinnamyl(3,5-dimethoxyphenyl)carbamate (1ac). Prepared from methyl (3,5-dimethoxyphenyl)carbamate (0.30 g, 1.43 mmol), NaH (60% in mineral oil) (62.9 mg, 1.57 mmol) and cinnamyl chloride (0.24 mL, 1.71 mmol). The reaction mixture was stirred at room temperature for 3 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 7/3) **1ac** was obtained as an oil (0.45 g, 70 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 9H,), 4.40 (d, J = 6.2 Hz, 2H), 6.07-6.60 (m, 5H,), 7.12-7.41 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 52.9, 53.0, 55.4, 98.8, 106.5, 125.1, 126.5, 127.7, 128.6, 132.6, 136.7, 143.7, 155.9, 160.9 ppm; IR (ATR): 1702 cm^{-1}; MS (EI) *m/z* (rel intensity): 327.2 (M^+, 16), 236.1 (56), 117.1 (100); HRMS (ESI-TOF): calcd. for $C_{19}H_{22}NO_4$: 328.1549 [MH^+]; found, 328.1565.

Methyl *(Z)*-(3,5-dimethoxyphenyl)(3-phenylallyl) carbamate (*(Z)*-1ac). Prepared from methyl (3,5-dimethoxyphenyl)carbamate (0.45 g, 2.1 mmol), NaH (60% in mineral oil) (93.5 mg, 2.3 mmol) and (*Z*)-(3-chloroprop-1-en-1-yl)benzene[29] (0.39 g, 2.5 mmol). The reaction mixture was stirred at room temperature for 5.5 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 8/2) afforded ***(Z)*-1ac** as a solid (0.54 g, 78 %): mp (CH_2Cl_2) 65-67 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 6H), 3.74 (s, 3H), 4.60 (dd, J = 6.3, 1.8 Hz, 2H), 5.84 (dt, J = 12.0, 6.3 Hz, 1H), 5.35-5.38 (m, 1H), 6.39 (d, J = 2.0 Hz, 2H), 6.58 (d, J = 12.0 Hz, 1H), 7.11-7.35 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 48.7, 53.0, 55.3, 98.8, 105.1, 127.1, 128.3, 128.7, 128.8, 131.1, 136.5, 143.5, 155.8, 160.8 ppm; IR (ATR): 1690 cm^{-1}; MS (ESI) *m/z* (rel intensity): 328.2 (MH^+, 60), 224.1 (100); HRMS (ESI-TOF): calcd. for $C_{19}H_{22}NO_4$: 328.1549 [MH^+]; found, 328.1548.

Methyl (3,5-dimethoxyphenyl)(2-methylallyl)carbamate (1ar). Prepared from methyl (3,5-dimethoxyphenyl)carbamate (0.22 g, 1.05 mmol), NaH (60% in mineral oil) (46.3 mg, 1.16 mmol) and 3-chloro-2-methylprop-1-ene (0.12 mL, 1.26 mmol). The reaction mixture was stirred at room temperature for 3 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 6/4) **1ar** was obtained as an oil (0.25 g, 89 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (s,

3H), 3.71 (s, 3H), 3.76 (s, 6H), 4.18 (s, 2H), 4.80-4.88 (m, 2H), 6.30-6.36 (m, 1H), 6.41 (d, J = 1.5 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 20.1, 53.0, 55.4, 56.2, 98.2, 104.9, 112.0, 141.2, 143.9 (C_1), 156.0, 160.6 ppm; IR (ATR): 1706 cm^{-1}; MS (EI) *m/z* (rel intensity): 265.2 (M^+, 80), 250.2 (100); HRMS (ESI-TOF): calcd. for $C_{14}H_{20}NO_4$: 266.1392 [MH^+]; found, 266.1401.

***tert*-Butyl allyl(3,5-dimethoxyphenyl)carbamate (1ba).** Prepared from *tert*-butyl (3,5-dimethoxyphenyl)carbamate (0.47 g, 1.86 mmol), NaH (60% in mineral oil) (82.0 mg, 2.05 mmol) and allyl chloride (0.18 mL, 2.24 mmol). The reaction mixture was stirred at room temperature for 4 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 9/1) **1ba** was obtained as an oil (0.39 g, 72 %): ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.76 (s, 6H), 4.20 (d, J = 5.5 Hz, 2H), 5.07-5.23 (m, 2H), 5.92 (qd, 1H, J = 10.6, 5.5 Hz), 6.31 (t, J = 2.0 Hz, 1H), 6.42 (d, J = 2.0 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 28.3, 53.0, 55.3, 80.4, 97.9, 104.8, 116.3, 134.4, 144.4, 154.2, 160.5 ppm; IR (ATR): 1699 cm^{-1}; MS (ESI) *m/z* (rel intensity): 294.2 (MH^+, 6), 238.1 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{24}NO_4$: 294.1705 [MH^+]; found, 294.1715.

***tert*-Butyl cinnamyl(3,5-dimethoxyphenyl)carbamate (1bc).** Prepared from *tert*-butyl (3,5-dimethoxyphenyl)carbamate (0.63 g, 2.50 mmol), NaH (60% in mineral oil) (0.11 g, 2.75 mmol) and cinnamyl chloride (0.42 mL, 3.00 mmol). The reaction mixture was stirred at room temperature for 7.5 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 9/1) **1bc** was obtained as a solid (0.91 g, 98 %): mp (CH_2Cl_2) 63-64 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (s, 9H), 3.76 (s, 6H), 4.40 (d, J = 6.2 Hz, 2H), 6.22-6.38 (m, 2H), 6.39-6.57 (m, 3H,), 7.18-7.42 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 28.3, 52.6, 55.4, 80.5, 98.1, 105.0, 125.8, 126.4, 127.5, 128.5, 131.9, 136.9, 144.6, 154.3, 160.6 ppm; IR (ATR): 1685 cm^{-1}; MS (ESI) *m/z* (rel intensity): 370.2 (MH^+, 6), 314.1 (100); HRMS (ESI-TOF): calcd. for $C_{22}H_{28}NO_4$: 370.2018 [MH^+]; found, 370.2024.

Benzyl allyl(3,5-dimethoxyphenyl)carbamate (1ca). Prepared from benzyl (3,5-dimethoxyphenyl)carbamate (0.40 g, 1.41 mmol), NaH (60% in mineral oil) (61.9 mg, 1.55 mmol) and allyl chloride (0.14 mL, 1.69 mmol). The reaction mixture was stirred at room temperature for 5 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 9/1) **1ca** was

obtained as an oil (0.40 g, 86 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 6H), 4.28 (dt, J = 5.8, 1.4 Hz, 2H), 5.12- 5.24 (m, 4H), 5.85-6.03 (m, 1H), 6.37 (t, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 2H), 7.25-7.41 (m, 5H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 53.3, 55.3, 67.3, 98.8, 106.1, 117.1, 127.8, 127.9, 128.4, 133.9, 136.6, 143.8, 155.1, 160.7 ppm; IR (ATR): 1702 cm^{-1}; MS (ESI) *m/z* (rel intensity): 328.2 (MH^+, 93); HRMS (ESI-TOF): calcd. for $C_{19}H_{22}NO_4$: 328.1541 [MH^+]; found, 328.1558.

***N*-Allyl-*N*-(3,5-dimethoxyphenyl)acetamide (1da).** Prepared from *N*-(3,5-dimethoxyphenyl)acetamide (0.28 g, 1.43 mmol), NaH (60% in mineral oil) (62.9 mg, 1.57 mmol) and allyl chloride (0.14 mL, 1.72 mmol). The reaction mixture was stirred at room temperature for 3 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 5/5) **1da** was obtained as an oil (0.32 g, 97 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H), 3.67 (s, 6H), 4.26 (d, J = 6.2 Hz, 2H), 5.02- 5.20 (m, 2H), 5.87 (ddt, J = 16.8, 10.7, 6.2 Hz, 1H), 6.31 (d, J = 2.1 Hz, 2H), 6.42 (t, J = 2.1 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 22.5, 51.8, 55.4, 99.5, 106.4, 117.7, 133.3, 144.7, 161.2, 169.9 ppm; IR (ATR): 1652 cm^{-1}; MS (EI) *m/z* (rel intensity): 235.1 (M^+, 84), 192.1 (100); HRMS (CI-TOF): *m/z* calcd. for $C_{13}H_{18}NO_3$: 236.1287 [MH^+]; found, 236.1294.

(1*R*,2*S*,5*R*)-2-Isoprpyl-5-methylcyclohexyl allyl(3,5-dimethoxyphenyl)carbamate (1ga). Prepared from (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl)carbamate (**A**, see below) (0.45 g, 1.36 mmol), NaH (60% in mineral oil) (59.6 mg, 1.49 mmol) and allyl chloride (0.13 mL, 1.63 mmol). The reaction mixture was stirred at room temperature for 4 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 9/1) **1ga** was obtained as an oil (0.37 g, 72 %): $[\alpha]_D^{20}$ –36.9 (c 2.75, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73-0.93 (m, 10H), 0.93-1.14 (m, 2H), 1.22-1.38 (m, 1H), 1.39-1.57 (m, 1H), 1.58-1.71 (m, 2H), 1.86-1.99 (m, 1H), 2.05-2.16 (m, 1H), 3.76 (s, 6H), 4.23 (d, J = 5.6 Hz, 2H), 4.62 (td, J = 10.8, 4.3 Hz, 1H), 5.11-5.22 (m, 2H), 5.84-6.00 (m, 1H), 6.32 (t, J = 2.2 Hz, 1H), 6.42 (d, J = 2.2 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 16.3, 20.8, 22.0, 23.4, 26.2, 31.4, 34.3, 41.2, 47.1, 53.1, 55.3, 75.8, 98.4, 104.9, 116.7, 134.2 , 144.2, 155.0, 160.6 ppm; IR (ATR): 1700 cm^{-1}; MS (ESI) *m/z* (rel intensity): 376.2 (MH^+, 23), 238.1 (87); HRMS (ESI-TOF): calcd. for $C_{22}H_{34}NO_4$: 376.2488 [MH^+]; found, 376.2491.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl)carbamate (**A**): Over a solution of commercially available 3,5-dimethoxyaniline (0.67 g, 4.4 mmol) and pyridine (0.69 g, 8.8 mmol) in dry THF (20 mL) under argon atmosphere, (1*R*)-(-)-menthyl chloroformate (1.1 mL, 4.8 mmol) was added dropwise. The reaction was stirred for 16 h at room temperature and afterwards the solvent was removed under reduced pressure. The crude reaction was dissolved in CH_2Cl_2 (30 mL) and washed with a 10% aqueous solution of HCl (2 × 15 mL) and with water (15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) affording the title compound as a solid (1.1 g, 75 %): mp (CH_2Cl_2) 89-91 ºC; $[\alpha]_D^{20}$ –118.4 (c 1.15 , CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75-0.91 (m, 10H), 0.93-1.13 (m, 2H), 1.24-1.38 (m, 1H), 1.38-1.57 (m, 1H), 1.60-1.70 (m, 2H), 1.88-2.02 (m, 1H), 2.01-2.11 (m, 1H), 3.74 (s, 6H), 4.62 (td, J = 10.8, 4.3 Hz, 1H), 6.16 (t, J = 2.2 Hz, 1H), 6.66 (d, J = 2.2 Hz, 2H), 6.91 (br s, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 16.4, 20.8, 22.0, 23.5, 26.2, 31.4, 34.2, 41.3, 47.2, 55.3, 75.1, 95.7, 96.7, 140.2, 153.4, 161.1 ppm; IR (ATR): 3357, 1739 cm^{-}; MS (ESI) *m/z* (rel intensity): 358.2 (MNa^+, 100), 198.1 (18); HRMS (ESI-TOF): calcd. for $C_{19}H_{29}NO_4Na$: 358.1994 [MNa^+]; found, 358.1993.

(1*R*,2*S*,5*R*)-2-Isoprpyl-5-methylcyclohexyl [(*E*)-but-2-en-1-yl](3,5-dimethoxyphenyl)carbamate (1gb). Prepared from **A** (0.42 g, 1.3 mmol), NaH (60% in mineral oil) (55.4 mg, 1.4 mmol) and crotyl chloride (0.15 mL, 1.5 mmol). The reaction mixture was stirred at room temperature for 7 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 9/1) **1gb** was obtained as an oil (0.40 g, 82 %): $[\alpha]_D^{20}$ –42.9 (c 0.74, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77-0.92 (m, 10H), 0.92-1.09 (m, 2H), 1.24-1.36 (m, 1H), 1.42-1.54 (m, 1H), 1.57-1.66 (m, 2H), 1.67 (d, J = 4.0 Hz, 3H), 1.86-1.96 (m, 1H), 2.07-2.15 (m, 1H), 3.77 (s, 6H), 4.09-4.34 (m, 2H), 4.61-4.72 (dt, J = 10.8, 4.3 Hz, 1H), 5.49-5.65 (m, 2H), 6.32 (t, J = 2.0 Hz, 1H), 6.40 (br s, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 16.3, 17.7, 20.9, 22.1, 23.4, 26.2, 31.4, 34.3, 41.3, 47.2, 52.5, 55.4, 75.7, 98.4, 105.1, 126.8, 128.2, 144.3, 155.0, 160.5 ppm; IR (ATR): 1695 cm^{-1}; MS (ESI) *m/z* (rel intensity): 412.2 (MNa^+, 100); HRMS (ESI-TOF): calcd. for $C_{23}H_{35}NO_4Na$: 412.2464 [MNa^+]; found, 412.2455.

(1*R*,2*S*,5*R*)-2-Isoprpyl-5-methylcyclohexyl cinnamyl(3,5-dimethoxyphenyl)carbamate (1gc). Prepared from **A** (0.21 g, 0.64 mmol), NaH (60% in mineral oil) (28.1 mg, 0.70 mmol) and cinnamyl chloride (0.11 mL, 0.77 mmol). The reaction mixture was stirred at room temperature for 7 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 9/1) **1gc** was obtained as an oil (0.21 g, 71 %): $[\alpha]_D^{20}$ –95.2 (c 1.05, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77-0.94 (m, 10H), 0.94-1.15 (m, 2H), 1.26-1.39 (m, 1H), 1.41-1.58 (m, 1H), 1.60-1.75 (m, 2H), 1.88-2.06 (m, 1H), 2.10-2.20 (m, 1H), 3.75 (s, 6H), 4.31-4.49 (m, 2H), 4.61-4.72 (m, 1H), 6.25-6.37 (m, 2H), 6.43-6.54 (m, 3H), 7.19-7.38 (m, 5H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 16.3, 20.8, 22.1, 23.4, 26.3, 31.4, 34.3, 41.3, 47.2, 52.7, 55.4, 75.9, 98.6, 105.0, 125.5, 126.4, 127.6, 128.5, 132.1, 136.8, 144.2, 155.1, 160.7 ppm; IR (ATR): 1695 cm^{-1}; MS (ESI) *m/z* (rel intensity): 474.3 (MNa^+, 77), 314.1 (10) ; HRMS (ESI-TOF): calcd. for $C_{28}H_{37}NO_4Na$: 474.2620 [MNa^+]; found, 474.2623.

***N*-allyl-3,5-dimethoxy-*N*-methylaniline (1ea).** (Scheme S1c) Over a solution of 3,5-dimethoxy-*N*-methylaniline (0.20 g, 1.22 mmol) in DMSO (5 mL), powder KOH (0.14 g, 2.47 mmol) was added. After 15 min, allyl bromide (0.13 mL, 1.46 mmol) was added dropwise at room temperature and the reaction was heated at 50 ºC (heating block with temperature control) for 1 h. Then, water (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **1ea** as an oil (0.15 g, 60 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.94 (s, 3H), 3.79 (s, 6H), 3.91 (dt, J = 5.1, 1.6 Hz, 2H), 5.15-5.21 (m, 2H), 5.85 (ddt, J = 17.0, 10.2, 5.1 Hz), 5.93 (s, 3H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 38.2, 55.2, 55.3, 88.6, 91.8, 116.2, 133.8, 151.4, 161.6 ppm; IR (ATR): 1612 cm^{-1}; MS (CI) *m/z* (rel intensity): 208.1 (MH^+, 97), 207.1 (100), 176.1 (32); HRMS (CI-TOF): calcd. for $C_{12}H_{18}NO_2$: 208.1338 [MH^+]; found, 208.1320.

Alkylation reactions. Synthesis of tosylamides 1fa-1fd. General procedure (Scheme S1d). Over a solution of *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (1 mmol) in dry acetone (20 mL), K_2CO_3 (2.5 mmol) and the corresponding allyl bromide (1.5 mmol) were added under argon atmosphere. The reaction mixture was heated at reflux (heating block) for 16 h and then, it was allowed

to cool down to room temperature. Afterwards, CH_2Cl_2 (20 mL) was added and the mixture was washed with water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, hexane/AcOEt 8/2) afforded the corresponding *N*-allyl-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamides **1fa-1fd**.

***N*-allyl-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (1fa).** Prepared from *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (0.40 g, 1.32 mmol), K_2CO_3 (0.45 g, 3.29 mmol) and allyl bromide (0.17 mL, 1.97 mmol). After work-up and purification by flash column chromatography **1fa** was obtained as a solid (0.41 g, 89 %): mp (CH_2Cl_2) 82-84 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.70 (s, 6H), 4.13 (d, J = 6.1 Hz, 2H), 5.00-5.18 (m, 2H), 5.64-5.86 (m, 1H), 6.21 (d, J = 1.8 Hz, 1H), 6.37 (t, J = 1.8 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 21.5, 53.6, 55.4, 100.0, 107.0, 118.7, 127.8, 129.4, 132.8, 135.5, 140.9, 143.5, 160.6 ppm; IR (ATR): 1345 cm^{-1}, 1155 cm^{-1}; MS (ESI) *m/z* (rel intensity): 370.1 (MNa^+, 100), 348.1 (MH^+, 52), 193.1 (57); HRMS (ESI-TOF): calcd. for $C_{18}H_{21}NO_4SNa$: 370.1089 [MNa^+]; found, 370.1091.

***(E)*-*N*-(but-2-en-1-yl)-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (1fb).** Prepared from *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (0.30 g, 0.98 mmol), K_2CO_3 (0.34 g, 2.45 mmol) and crotyl bromide (0.18 mL, 1.47 mmol). After work-up and purification by flash column chromatography **1fb** was obtained as a solid and as a mixture of rotamers in a 83:17 ratio (0.30 g, 83 %): mp (CH_2Cl_2) 101-102 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59-1.54 (m, 3H, minor rotamer), 1.55-1.59 (m, 3H, major rotamer), 2.41 (s, 3H, both rotamers), 3.70 (s, 6H, both rotamers), 4.02-4.09 (m, 2H, major rotamer), 4.14-4.20 (m, 2H, minor rotamer), 5.30-5.58 (m, 2H, both rotamers), 6.19 (d, J = 2.3 Hz, 2H, major rotamer), 6.21 (d, J = 2.3 Hz, 2H, minor rotamer), 6.36 (t, J = 2.3 Hz, 1H, both rotamers), 7.25 (d, J = 8.3 Hz, 2H, both rotamers), 7.54 (d, J = 8.3 Hz, 2H, both rotamers); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 12.9 (minor rotamer), 17.7 (major rotamer), 21.5 (both rotamers), 47.4 (minor rotamer), 53.1 (major rotamer), 55.4 (both rotamers), 100.0 (both rotamers), 106.9 (minor rotamer),

107.1 (major rotamer), 124.7 (minor rotamer), 125.5 (major rotamer), 127.8 (major rotamer), 128.4 (minor rotamer), 129.3 (major rotamer), 129.4 (minor rotamer), 130.2 (both rotamers), 135.8 (both rotamers), 141.1 (both rotamers), 143.3 (both rotamers), 160.5 (both rotamers) ppm; IR (ATR): 1285, 1160 cm^{-1}; MS (ESI) *m/z* (rel intensity): 384.1 (MNa^+, 100), 362.1 (MH^+, 78), 308.1 (24), 207.1 (59); HRMS (ESI-TOF): calcd. for $C_{19}H_{23}NO_4SNa$: 384.1246 [MNa^+]; found, 384.1241.

***N*-Cinnamyl- *N* -(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (1fc).** Prepared from *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (0.27 g, 0.87 mmol), K_2CO_3 (0.30 g, 2.16 mmol) and cinnamyl bromide (0.26 g, 1.30 mmol). After work-up and purification by flash column chromatography **1fc** was obtained as a solid (0.21 g, 58 %): mp (CH_2Cl_2) 123-126 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.68 (s, 6H), 4.32 (dd, J = 6.5, 1.0 Hz, 2H), 6.14 (dt, J = 15.8, 6.5 Hz, 1H), 6.28 (d, J = 2.2 Hz, 2H), 6.38 (t, J = 2.2 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 7.17-7.30 (m, 7H), 7.61 (d, J = 8.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 21.6, 53.4, 55.4, 100.1, 107.1, 124.2, 126.5, 127.8, 128.6, 129.5, 133.7, 135.7, 136.4, 141.1, 143.6, 160.7 ppm; IR (ATR): 1345, 1155 cm^{-1}; MS (ESI) *m/z* (rel intensity): 446.1 (MNa^+, 53), 424.2 (MH^+,100), 117.1 (89); HRMS (ESI-TOF): calcd. for $C_{24}H_{25}NNaO_4S$: 446.1402 [MNa^+]; found, 446.1397.

***(E)*-*N*-(3,5-dimethoxyphenyl)-4-methyl-*N*-(4-phenylbut-2-en-1-yl) benzene sulfonamide (1fd).** Prepared from *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (0.30 g, 0.99 mmol), K_2CO_3 (0.34 g, 2.47 mmol) and *(E)*-(4-bromobut-2-en-1-yl)benzene[30] (0.31 g, 1.48 mmol). After work-up and purification by flash column chromatography **1fd** was obtained as an oil (0.40 g, 92 %): ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.26 (d, J = 6.6 Hz, 2H), 3.67 (s, 6H), 4.16 (d, J = 6.4 Hz, 2H), 5.38-5.71 (m, 2H), 6.24 (d, J = 2.3 Hz, 2H), 6.42 (t, J = 2.3 Hz, 1H), 6.84-6.99 (m, 2H), 7.10-7.30 (m, 5H), 7.58 (d, J = 8.3 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 21.6, 38.4, 53.0, 55.4, 100.2, 107.3, 126.0, 126.1, 127.8, 128.4, 128.5, 129.5, 134.1, 135.7, 139.7, 140.9, 143.5, 160.7 ppm; IR (ATR): 1360, 1170 cm^{-1}; MS (ESI) *m/z* (rel intensity): 438.2 (MH^+, 100), 308.1 (25), 131.1 (22); HRMS (ESI-TOF): calcd. for $C_{25}H_{28}NO_4S$: 438.1739 [MH^+]; found, 438.1746.

Metathesis reactions. Synthesis of carbamates 1ad-1gl. General procedure (Scheme S2a). Two different procedures were employed depending on the styrene used: In case of a liquid styrene, a solution of allyl(3,5-dimethoxyphenyl)carbamate **1aa** or **1ga** (1 mmol) and the corresponding styrene (5 mmol) in dry CH_2Cl_2 (2.3 mL) was added *via cannula* over a solution of 2nd Generation Grubbs Catalyst (0.05 mmol) in dry CH_2Cl_2 (1.1 mL) under argon atmosphere. In case of a solid styrene, a solution of 2nd Generation Grubbs Catalyst (0.05 mmol) in dry CH_2Cl_2 (1.1 mL) was added *via cannula* over a solution of allyl(3,5-dimethoxyphenyl)carbamate **1aa** or **1ga** (1mmol) and the corresponding styrene (5 mmol) in dry CH_2Cl_2 (2.3 mL) under argon atmosphere. In both cases, the reaction mixture was stirred at reflux (heating block) for 24 h and the volatile compounds were evaporated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) to obtain the corresponding carbamates **1ad-1gl**.

Methyl (*E*)-(3,5-dimethoxyphenyl)[3-(*p*-tolyl)allyl]carbamate (1ad). Prepared from **1aa** (0.28 g, 1.13 mmol) and 4-methylstyrene (0.74 mL, 5.65 mmol) in dry CH_2Cl_2 (2.6 mL) and 2nd Generation Grubbs Catalyst (48.0 mg, 0.056 mmol) in dry CH_2Cl_2 (1.3 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **1ad** as a solid (0.27 g, 70 %): mp (CH_2Cl_2) 93-95 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.74 (s, 3H), 3.76 (s, 6H), 4.38 (d, J = 6.3 Hz, 2H), 6.26 (dt, J = 15.9, 6.3 Hz, 1H), 6.37 (t, J = 2.2 Hz, 1H), 6.40-6.50 (m, 3H), 7.11 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 21.2, 53.0, 55.4, 98.8, 106.5, 124.0, 126.4, 129.2, 132.5, 133.9, 137.5, 143.7, 155.8, 160.8 ppm; IR (ATR): 1690 cm^{-1}; MS (ESI) *m/z* (rel intensity): 343.2 342.2 (MH^+, 100), 224.1 (7); HRMS (ESI-TOF): calcd. for $C_{20}H_{24}NO_4$: 342.1705 [MH^+]; found, 342.1711.

Methyl (*E*)-(3,5-dimethoxyphenyl)[3-(*m*-tolyl)allyl]carbamate (1ae). Prepared from **1aa** (0.37 g, 1.49 mmol) and 3-methylstyrene (0.99 mL, 7.44 mmol) in dry CH_2Cl_2 (3.4 mL) and 2nd Generation Grubbs Catalyst (63.2 mg, 0.074 mmol) in dry CH_2Cl_2 (1.7 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **1ae** as an oil (0.31 g, 61 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.75 (s, 3H), 3.76 (s, 6H), 4.39 (d, J = 6.1 Hz, 2H), 6.22-6.50 (m,

5H), 6.99-7.29 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 21.4, 53.0, 55.4, 98.8, 106.4, 123.6, 124.8, 127.1, 128.4, 132.7, 136.6, 138.1, 143.7, 155.8, 160.8 ppm; IR (ATR): 1702 cm^{-1}; MS (ESI) *m/z* (rel intensity): 342.2 (MH^+, 100), 224.1 (12); HRMS (ESI-TOF): calcd. for $C_{20}H_{24}NO_4$: 342.1705 [MH^+]; found, 342.1714.

Methyl (*E*)-(3,5-dimethoxyphenyl)[3-(*o*-tolyl)allyl]carbamate (1af). Prepared from **1aa** (0.34 g, 1.36 mmol) and 2-methylstyrene (0.91 mL, 6.78 mmol) in dry CH_2Cl_2 (3.1 mL) and 2nd Generation Grubbs Catalyst (57.5 mg, 0.068 mmol) in dry CH_2Cl_2 (1.5 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **1af** as an oil (0.35 g, 75 %): ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.74 (s, 3H), 3.77 (s, 6H), 4.41 (dd, J = 6.4, 1.4 Hz, 2H), 6.15 (dt, J = 15.7, 6.4 Hz, 2H), 6.38 (t, J = 2.3 Hz, 1H), 6.43 (d, J = 2.3 Hz, 2H), 6.68 (d, J = 15.7 Hz, 1H), 7.10-7.19 (m, 3H), 7.37-7.43 (m, 1H); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 19.7, 53.0, 55.4, 98.8, 106.5, 125.9, 126.1, 126.4, 127.5, 130.2, 130.8, 135.4, 136.0, 143.6, 155.8, 160.8 ppm; IR (ATR): 1702 cm^{-1}; MS (ESI) *m/z* (rel intensity): 342.2 (MH^+, 100), 224.1 (13); HRMS (ESI-TOF): calcd. for $C_{20}H_{24}NO_4$: 342.1705 [MH^+]; found, 342.1712.

Methyl (*E*)-(3,5-dimethoxyphenyl)[3-(3-methoxyphenyl)allyl]carbamate (1ah). Prepared from **1aa** (0.13 g, 0.50 mmol) and 3-vinylanisole (0.35 mL, 2.52 mmol) in dry CH_2Cl_2 (1.1 mL) and 2nd Generation Grubbs Catalyst (21.4 mg, 0.025 mmol) in dry CH_2Cl_2 (0.6 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **1ah** as an oil (0.11 g, 61 %): ^1H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.75 (s, 6H), 3.80 (s, 3H), 4.38 (d, J = 5.9 Hz, 2H), 6.21-6.53 (m, 5H), 6.76-6.82 (m, 1H), 6.87-6.91 (m, 1H), 6.92-6.98 (m, 1H), 7.17-7.27 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 52.9, 53.0, 55.2, 55.4, 98.8, 106.4, 111.8, 113.3, 119.1, 125.4, 129.5, 132.5, 138.2, 143.7, 155.8, 159.8, 160.8 ppm; IR (ATR): 1706 cm^{-1}; MS (ESI) *m/z* (rel intensity): 358.2 (MH^+, 100), 224.1 (15); HRMS (ESI-TOF): calcd. for $C_{20}H_{24}NO_5$: 358.1654 [MH^+]; found, 358.1664.

Methyl (*E*)-[3-([1,1`-biphenyl]-4-yl)allyl](3,5-dimethoxyphenyl)carbamate (1ai). Prepared from **1aa** (0.35 g, 1.41 mmol) and 4-vinylbiphenyl (1.27 mL, 7.05 mmol) in dry CH_2Cl_2 (3.2 mL) and 2nd

Generation Grubbs Catalyst (59.8 mg, 0.070 mmol) in dry CH_2Cl_2 (1.6 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **1ai** as a solid (0.23 g, 40 %): mp (CH_2Cl_2) 122-125 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.77 (s, 6H), 4.42 (dd, J = 6.2, 0.9 Hz, 2H), 6.28-6.58 (m, 5H), 7.30-7.38 (m, 1H), 7.40-7.48 (m, 4H), 7.53-7.63 (m, 4H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 53.0, 55.4, 98.8, 106.5, 125.2, 126.9, 127.0, 127.2, 127.3, 128.8, 132.2, 135.7, 140.4, 140.6, 143.7, 155.9, 160.8 ppm; IR (ATR): 1706 cm^{-1}; MS (ESI) *m/z* (rel intensity): 404.2 (MH^+, 100), 193.1 (8); HRMS (ESI-TOF): calcd. for $C_{25}H_{26}NO_4$: 404.1862 [MH^+]; found, 404.1859.

Methyl (*E*)-{3-[4-(*tert*-butyl)phenyl]allyl}(3,5-dimethoxyphenyl)carbamate (1aj). Prepared from **1aa** (0.25 g, 1.01 mmol) and 4-*tert*-butylstyrene (0.92 mL, 5.03 mmol) in dry CH_2Cl_2 (2.3 mL) and 2nd Generation Grubbs Catalyst (42.6 mg, 0.050 mmol) in dry CH_2Cl_2 (1.1 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **1aj** as a solid (0.26 g, 67 %): mp(CH_2Cl_2) 108-111 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 9H), 3.73 (s, 3H), 3.76 (s, 6H), 4.37 (d, J = 5.9 Hz, 2H), 6.15-6.57 (m, 5H), 7.20-7.39 (m, 4H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 31.3, 34.4, 53.0, 55.4, 98.7, 106.4, 124.2, 125.5, 126.2, 132.4, 133.9, 143.7, 150.8, 155.8, 160.8 ppm; IR (ATR): 1706 cm^{-1}; MS (ESI) *m/z* (rel intensity): 384.2 (MH^+, 86), 173.1 (20); HRMS (ESI-TOF): calcd. for $C_{23}H_{30}NO_4$: 384.2175 [MH^+]; found, 384.2183.

Methyl (*E*)-(3,5-dimethoxyphenyl)[3-(4-fluorophenyl)allyl]carbamate (1ak). Prepared from **1aa** (0.31 g, 1.25 mmol) and 4-fluorostyrene (0.74 mL, 6.23 mmol) in dry CH_2Cl_2 (2.8 mL) and 2nd Generation Grubbs Catalyst (52.9 mg, 0.062 mmol) in dry CH_2Cl_2 (1.4 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **1ak** as a solid (0.24 g, 56 %): mp (CH_2Cl_2) 90-91 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.75 (s, 6H), 4.36 (dd, J = 6.3, 1.1 Hz, 2H), 6.21 (dt, J = 15.8, 6.3 Hz, 1H), 6.37 (t, J = 2.2 Hz, 1H), 6.39-6.49 (m, 3H), 6.93-7.02 (m, 2H), 7.27-7.34 (m, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 52.9, 53.0, 55.4, 98.7, 105.5, 115.4 (d, J = 21.6 Hz), 124.8 (d, J = 2.0 Hz), 128.0 (d, J = 8.7 Hz), 131.4, 132.9 (d, J = 3.8 Hz), 143.7, 155.8, 160.8, 162.3 (d, J = 247.4 Hz) ppm; IR (ATR): 1695 cm^{-1}; MS (ESI) *m/z* (rel intensity): 346.1 (MH^+, 100), 224.1 (12); HRMS (ESI-TOF): calcd. for $C_{19}H_{21}FNO_4$: 346.1455 [MH^+]; found: 346.1453.

Methyl *(E)*-(3,5-dimethoxyphenyl)[3-(naphthalen-1-yl)allyl]carbamate (1al). Prepared from **1aa** (0.30 g, 1.21 mmol) and 1-vinylnaphthalene (0.90 mL, 6.06 mmol) in dry CH_2Cl_2 (2.8 mL) and 2nd Generation Grubbs Catalyst (51.4 mg, 0.061 mmol) in dry CH_2Cl_2 (1.4 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **1al** as an oil (0.32 g, 70 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.80 (s, 6H), 4.55 (d, J = 6.4 Hz, 2H), 6.35 (dt, J = 15.9, 6.6 Hz, 1H), 6.45 (t, J = 2.0 Hz, 1H), 6.54 (d, J = 2.0 Hz, 2H), 7.26 (d, J = 15.9 Hz, 1H), 7.42-7.46 (m, 1H), 7.46-7.54 (m, 2H), 7.56-7.61 (m, 1H), 7.76-7.82 (m, 1H), 7.83-7.89 (m, 1H), 7.96-8.05 (m, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 53.1, 55.5, 99.0, 105.7, 123.9, 124.1, 125.7, 125.9, 126.1, 128.1, 128.3, 128.6, 130.4, 131.2, 133.6, 134.6, 143.7, 155.9, 161.0 ppm; IR (ATR): 1702 cm^{-1}; MS (ESI) *m/z* (rel intensity): 400.2 (MNa^+, 100), 378.2 (MH^+, 94), 224.1 (70), 167.1 (65); HRMS (ESI-TOF): calcd. for $C_{23}H_{24}NO_4$: 378.1705 [MH^+]; found, 378.1703.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl) [(*E*)-3-(naphthalene-1-yl) allyl]carbamate (1gl). Prepared from **1ga** (0.28 g, 0.74 mmol) and 1-vinylnaphthalene (0.55 mL, 3.71 mmol) in dry CH_2Cl_2 (1.7 mL) and 2nd Generation Grubbs Catalyst (31.5 mg, 0.037 mmol) in dry CH_2Cl_2 (0.84 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **1gl** as an oil (0.23 g, 62 %): $[\alpha]_D^{20}$ = -114.2 (c 0.53, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78-0.93 (m, 10H), 0.96-1.16 (m, 2H), 1.29-1.40 (m, 1H), 1.42-1.55 (m, 1H), 1.61-1.74 (m, 2H), 1.89-2.04 (m, 1H), 2.11-2.23 (m, 1H), 3.77 (s, 6H), 4.52 (dd, J = 6.1, 1.2 Hz, 2H), 4.69 (td, J = 10.8, 4.3 Hz, 1H), 6.19-6.58 (m, 4H), 7.23 (d, J = 15.7 Hz, 1H), 7.41-7.62 (m, 4H), 7.74-7.92 (m, 2H), 7.97-8.07 (m, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 16.4, 20.8, 22.1, 23.4, 26.3, 31.4, 34.3, 41.3, 47.2, 52.8, 55.4, 76.0, 98.8, 105.2, 123.9, 124.0, 125.6, 125.8, 126.0, 127.9, 128.5, 128.7, 129.8, 131.2, 133.6, 134.7, 144.1, 155.1, 161.7 ppm; IR (ATR): 1700 cm^{-1}; MS (ESI) *m/z* (rel intensity): 502.3 (MH^+, 36), 364.2 (100); HRMS (ESI-TOF): calcd. for $C_{32}H_{40}NO_4$: 502.2957 [MH^+]; found, 502.2961.

Metathesis reactions. Synthesis of esters 1am-1bm. General procedure (Scheme S2b). To a solution of the corresponding carbamate **1aa-1ba** (1 mmol) and acrylate (20 mmol) in dry CH_2Cl_2 (28.9 mL), a solution of 2nd Generation Grubbs Catalyst (0.05 mmol) in dry CH_2Cl_2 (8.1 mL) was added *via*

cannula, under argon atmosphere. The reaction mixture was stirred at reflux (heating block) for 7 h and it was allowed to cool down to room temperature. Afterwards, the solvent was evaporated *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt) afforded the corresponding esters **1am-1bm**.

Methyl *(E)*-4-[(3,5-dimethoxyphenyl)(methoxycarbonyl)amino]but-2-enoate (1am). Prepared from **1aa** (0.24 g, 0.95 mmol) and methyl acrylate (1.7 mL, 18.9 mmol) in dry CH_2Cl_2 (27.3 mL) and 2nd Generation Grubbs Catalyst (40.2 mg, 0.047 mmol) in dry CH_2Cl_2 (7.6 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) **1am** was obtained as an oil (0.27 g, 91 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.68 (s, 3H), 3.71 (s, 6H), 4.33 (dd, J = 5.5, 1.7 Hz, 2H), 5.90 (dt, J = 15.7, 1.7 Hz, 1H), 6.26-6.38 (m, 3H), 6.92 (dt, J = 15.7, 5.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 51.5, 51.6, 53.1, 55.3, 98.7, 105.0, 122.2, 143.3, 143.4, 155.5, 160.9, 166.3 ppm; IR (ATR): 1710 cm^{-1}; MS (ESI) *m/z* (rel intensity): 310.1 (MH^+, 100), 278.1 (23); HRMS (ESI-TOF): calcd. for $C_{15}H_{20}NO_6$: 310.1291 [MH^+]; found, 310.1300.

Ethyl *(E)*-4-[(3,5-dimethoxyphenyl)(methoxycarbonyl)amino]but-2-enoate (1an). Prepared from **1aa** (0.26 g, 1.04 mmol) and ethyl acrylate (2.3 mL, 20.8 mmol) in dry CH_2Cl_2 (30.1 mL) and 2nd Generation Grubbs Catalyst (44.2 mg, 0.052 mmol) in dry CH_2Cl_2 (8.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) **1an** was obtained as an oil (0.33 g, 99 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3H), 3.70 (s, 3H), 3.75 (s, 6H), 4.16 (q, J = 7.1 Hz, 2H), 4.36 (dd, J = 5.5, 1.7 Hz, 2H), 5.92 (dt, J = 15.7, 1.7 Hz, 1H), 6.28-6.41 (m, 3H), 6.92 (dt, J = 15.7, 5.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 14.2, 51.6, 53.2, 55.4, 60.5, 98.7, 106.0, 122.6, 143.2, 143.4, 155.6, 160.9, 165.9 ppm; IR (ATR): 1710 cm^{-1}; MS (ESI) *m/z* (rel intensity): 324.1 (MH^+, 100), 278.1 (9); HRMS (ESI-TOF): calcd. for $C_{16}H_{22}NO_6$: 324.1447 [MH^+]; found: 324.1454.

Butyl *(E)*-4-[(3,5-dimethoxyphenyl)(methoxycarbonyl)amino]but-2-enoate (1ao). Prepared from **1aa** (0.31 g, 1.25 mmol) and *n*-butyl acrylate (3.6 mL, 24.9 mmol) in dry CH_2Cl_2 (36.0 mL) and 2nd Generation Grubbs Catalyst (52.9 mg, 0.062 mmol) in dry CH_2Cl_2 (10.0 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) **1ao** was obtained as an oil (0.40 g, 91

%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3H), 1.25-1.45 (m, 2H), 1.53-1.68 (m, 2H), 3.67 (s, 3H), 3.71 (s, 6H), 4.08 (t, J = 6.7 Hz, 2H), 4.33 (dd, J = 5.4, 1.4 Hz, 2H), 5.89 (d, J = 15.7 Hz, 1H), 6.26-6.36 (m, 3H), 6.90 (dt, J = 15.7, 5.4 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 13.7, 19.1, 30.6, 51.6, 53.1, 55.3, 64.3, 98.7, 105.1, 122.6, 143.2 (C_1), 143.4, 155.6, 160.9, 166.0 ppm; IR (ATR): 1710 cm^{-1}; MS (ESI) *m/z* (rel intensity): 352.2 (MH^+, 100), 278.1 (5); HRMS (ESI-TOF): calcd. for $C_{18}H_{26}NO_6$: 352.1760 [MH^+]; found: 352.1761.

***tert*-Butyl *(E)*-4-[(3,5-dimethoxyphenyl)(methoxycarbonyl)amino]but-2-enoate (1ap).** Prepared from **1aa** (0.23 g, 0.91 mmol) and *tert*-butyl acrylate (2.7 mL, 18.3 mmol) in dry CH_2Cl_2 (26.4 mL) and 2nd Generation Grubbs Catalyst (38.8 mg, 0.046 mmol) in dry CH_2Cl_2 (7.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) **1ap** was obtained (0.31 g, 99%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.68 (s, 3H), 3.73 (s, 6H), 4.32 (dd, J = 5.5, 1.7 Hz, 2H), 5.82 (dt, J = 15.7, 1.7 Hz, 1H), 6.28-6.38 (m, 3H), 6.81 (dt, J = 15.7, 5.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 28.0, 51.5, 53.1, 55.3, 80.5, 98.7, 105.0, 124.3, 141.9, 143.5, 155.6, 160.8, 165.2 ppm; IR (ATR): 1702 cm^{-1}; MS (ESI) *m/z* (rel intensity): 352.2 (MH^+, 11), 296.1 (100); HRMS (ESI-TOF): calcd. for $C_{18}H_{26}NO_6$: 352.1760 [MH^+]; found, 352.1760.

Benzyl *(E)*-4-[(3,5-dimethoxyphenyl)(methoxycarbonyl)amino]but-2-enoate (1aq). Prepared from **1aa** (0.20 g, 0.81 mmol) and benzyl acrylate (2.4 mL, 16.2 mmol) in dry CH_2Cl_2 (23.4 mL) and 2nd Generation Grubbs Catalyst (34.4 mg, 0.041 mmol) in dry CH_2Cl_2 (6.5 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) **1aq** was obtained as an oil (0.31 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.71 (s, 6H), 4.37 (d, J = 4.1 Hz, 2H), 5.15 (s, 2H,), 5.99 (d, J = 15.7 Hz, 1H), 6.35 (br s, 1H), 6.38 (br s, 2H), 6.91-7.08 (m, 1H), 7.20-7.37 (m, 5H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 51.6, 53.1, 55.3, 66.3, 98.8, 105.1, 122.3, 128.2, 128.5, 135.9, 143.4, 144.0, 155.6, 160.9, 165.7 ppm; IR (ATR): 1710 cm^{-1}; MS (ESI) *m/z* (rel intensity): 408.1 (MNa^+, 100), 386.2 (MH^+, 60), 354.1 (37), 3; HRMS (ESI-TOF): calcd. for $C_{21}H_{23}NO_6Na$: 408.1423 [MNa^+]; found, 408.1420.

Methyl *(E)*-4-[(*tert*-butoxycarbonyl)(3,5-dimethoxyphenyl)amino]but-2-enoate (1bm). Prepared from **1ba** (0.26 g, 0.88 mmol) and methyl acrylate (1.6 mL, 17.5 mmol) in dry CH_2Cl_2 (25.3 mL) and 2nd Generation Grubbs Catalyst (37.2 mg, 0.044 mmol) in dry CH_2Cl_2 (7.1 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) **1bm** was obtained as an oil (0.26 g, 86 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.72 (s, 3H), 3.75 (s, 6H), 4.34 (dd, J = 5.2, 1.8 Hz, 2H), 5.93 (dt, J = 15.7, 1.8 Hz, 1H), 6.30 (t, J = 2.2 Hz, 1H), 6.36 (d, J = 2.2 Hz, 2H), 6.97 (dt, J = 15.7, 5.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 28.3, 51.3, 51.6, 55.4, 81.0, 98.1, 104.7, 121.7, 144.1, 144.4, 154.0, 160.7, 166.5 ppm; IR (ATR): 1699 cm^{-1}; MS (ESI) *m/z* (rel intensity): 374.2 (MNa^+, 54), 352.2 (MH^+, 2), 252.1 (100); HRMS (ESI-TOF): calcd. for $C_{18}H_{25}NO_6Na$: 374.1580 [MNa^+]; found, 374.1584.

Reductive amination and protection. Synthesis of Methyl *(E)*-(3,5-dimethoxyphenyl)[3-(4-methoxyphenyl)allyl]carbamate (1ag) (Scheme S3). Over a solution of commercially available 3,5-dimethoxyaniline (0.53 g, 3.47 mmol) in dry Et_2O (17 mL) *trans-p*-methoxycinnamaldehyde (0.56 g, 3.47 mmol) and anhydrous $MgSO_4$ (4 g) were added under argon atmosphere. The reaction mixture was stirred at room temperature for 16 h, it was filtered and the solvent was evaporated *in vacuo*. The crude imine was dissolved in dry MeOH (23 mL) and $NaBH_4$ (0.39 g, 10.4 mmol) was added portionwise under argon atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 3.5 h. Afterwards, a 1 M NaOH aqueous solution (15 mL) was added to quench the reaction and it was diluted with water (20 mL). The mixture was extracted with AcOEt (3 × 15 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. Flash column chromatography (silica gel, hexane/AcOEt 7/3) afforded **1hg** as an oil (0.64 g, 62 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 6H), 3.81 (s, 3H), 3.84-3.96 (m, 3H), 5.88 (d, J = 2.1 Hz, 2H), 5.93 (t, J = 2.1 Hz, 1H), 6.18 (dt, J = 15.8, 5.7 Hz, 1H), 6.57 (d, J = 15.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 46.3, 55.2, 55.3, 89.9, 91.9, 114.0, 124.6, 127.5, 129.7, 131.2, 150.1, 159.2, 161.8 ppm; IR (ATR): 3408 cm^{-1}; MS (ESI) *m/z* (rel intensity): 300.2 (MH^+, 37), 298.1 (44), 148.1 (7), 147.1 (100); HRMS (ESI-TOF): calcd. for $C_{18}H_{22}NO_3$: 300.1600 [MH^+];

found, 300.1600. Over a solution of **1hg** (0.51 g, 1.71 mmol) and freshly distilled pyridine (0.27 mL, 3.41 mmol) in dry THF (20 mL), methyl chloroformate (0.16 mL, 2.05 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 16 h and afterwards, the solvent was evaporated under reduced pressure. The crude reaction was dissolved in CH_2Cl_2 (30 mL) and washed with a 10% aqueous solution of HCl (2 × 15 mL) and with water (15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/AcOEt 7/3) afforded **1ag** as an oil (0.54 g, 89 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H), 3.74 (s, 6H), 3.77 (s, 3H), 4.32 (d, J = 6.4 Hz, 2H), 6.16 (dt, J = 15.8, 6.4 Hz, 1H), 6.33-6.48 (m, 4H), 6.83 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 52.9, 53.0, 55.2, 55.4, 98.8, 106.5, 114.0, 122.8, 127.6, 129.5, 132.1, 143.8, 155.8, 159.3, 160.8 ppm; IR (ATR): 1695 cm^{-1}; MS (ESI) *m/z* (rel intensity): 380.1 (MNa^+, 100), 358.2 (MH^+, 60), 224.1 (30), 147.1 (66); HRMS (ESI-TOF): calcd. for $C_{20}H_{23}NO_5Na$: 380.1474 [MNa^+]; found, 380.1473

5,7-dimethoxyquinoline (2). Over a solution of **1aa** (0.10 g, 0.41 mmol) in AcOH (1.7 mL), $PhCO_3{}^t$Bu (0.10 mL, 0.49 mmol), $Cu(OAc)_2$ (3.8 mg, 0.021 mmol), *p*-TsOH (79.5 mg, 0.41 mmol) and $PdCl_2(CH_3CN)_2$ (5.4 mg, 0.021 mmol) were added. The mixture was stirred at room temperature for 24 h, and then the solvent was removed under vacuum. The residue was dissolved in AcOEt (5 mL) and it was washed with a 2M aqueous solution of Na_2CO_3 (2 × 10 mL) and brine (2 × 10 mL). The aqueous phase was re-extracted with AcOEt (10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/AcOEt 5/5) afforded **2** as an oil (24.5 mg, 31%), whose data are coincidental to those reported:[31] ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3H), 3.96 (s, 3H), 6.51 (d, J = 1.7 Hz, 1H), 7.02 (d, J = 1.7 Hz, 1H), 7.22 (dd, J = 8.3, 4.3 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.79 (d, J = 4.3 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 55.6, 55.8, 98.1, 99.6, 116.8, 118.1, 130.6, 150.4, 150.9, 155.9, 161.2 ppm; IR (ATR): 1627 cm^{-1}; MS (EI) *m/z* (rel intensity): 189.1 (M^+, 100), 160 (17), 146 (15); HRMS (CI-TOF): calcd. for $C_{11}H_{12}NO_2$: 190.0868 [MH^+]; found: 190.0868.

Synthesis of 1,2-dihydroquinolines 3. General procedure. To a solution of the corresponding *N*-ptotected aniline **1** (1 mmol) in 1,4-dioxane (66.7 mL), *p*-TsOH (1 mmol), BQ (1 mmol) and $PdCl_2(CH_3CN)_2$ (0.05 or 0.1 mmol) were added and the reaction mixture was stirred at room temperature or 70 ºC (heating block with temperature control) for 1-16 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) affording the corresponding 1,2-dihydroquinolines **3.**

Methyl 5,7-dimethoxyquinoline-1(*2H*)-carboxylate (3aa) (Table 1, entry 1). Prepared from **1aa** (0.14 g, 0.57 mmol), *p*-TsOH (0.11 g, 0.57 mmol), BQ (61.6 mg, 0.57 mmol) and $PdCl_2(CH_3CN)_2$ (7.4 mg, 0.028 mmol) in dioxane (38 mL). The reaction mixture was stirred for 16 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **3aa** was obtained as an oil (0.12 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.80 (s, 6H), 4.32 (dd, J = 4.3, 1.7 Hz, 2H), 5.82 (dt, J = 9.6, 4.3 Hz, 1H), 6.24 (d, J = 2.3 Hz, 1H), 6.76 (dt, J = 9.6, 1.7 Hz, 1H), 6.85 (br s, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 43.2, 53.0, 55.4, 55.6, 94.8, 101.0, 111.2, 120.7, 120.8, 138.2, 154.7, 155.6, 159.4 ppm; IR (ATR): 1702 cm^{-1}; MS (EI) *m/z* (rel intensity): 249.1 (M^+, 79), 190.1 (100); HRMS (CI-TOF): calcd. for $C_{13}H_{16}NO_4$: 250.1079 [MH^+]; found, 250.1085.

***tert*-Butyl 5,7-dimethoxyquinoline-1(*2H*)-carboxylate (3ba)** (Table 1, entry 3). Prepared from **1ba** (0.12 g, 0.40 mmol), *p*-TsOH (75.2 mg, 0.40 mmol), BQ (42.3 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.3 mg, 0.040 mmol) in dioxane (26.3 mL). The reaction mixture was stirred for 1.5 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **3ba** was obtained as an oil (67.3 mg, 58 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 9H), 3.80 (s, 6H), 4.28 (dd, J = 4.3, 1.7 Hz, 2H), 5.82 (dt, J = 9.6, 4.3 Hz, 1H), 6.21 (d, J = 2.3 Hz, 1H), 6.72-6.79 (m, 1H), 6.82 (d, J = 2.3 Hz, 1H) ppm; ^{113}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 28.4, 42.8, 55.4, 55.6, 81.1, 94.5, 101.1, 111.2, 120.8, 121.0, 138.7, 153.1, 155.5, 159.1 ppm; IR (ATR): 1649 cm^{-1};

MS (ESI) *m/z* (rel intensity): 314.1 (MNa^+, 12), 292.2 (MH^+, 5), 236.1 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{21}NO_4Na$: 314.1368 [MNa^+]; found: 314.1370. In this reaction, *tert*-butyl 4,6-dimethoxy-2-methyl-1*H*-indole-1-carboxylate (**4ba**) was obtained as a by product (oil, 18.9 mg, 16 %): ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 9H), 2.35 (d, J = 1.3 Hz, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.30 (d, J = 2.0 Hz, 1H), 7.01-7.15 (m, 1H), 7.33-7.43 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 12.3, 28.2, 55.3, 55.6, 82.9, 91.4, 94.2, 114.8, 116.7, 120.0, 137.6, 149.9, 154.9, 158.8 ppm; IR (ATR): 1724 cm^{-1}; MS (ESI) *m/z* (rel intensity): 292.2 (MH^+, 58), 236.1 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{22}NO_4$: 292.1549 [MH^+]; found, 292.1557.

Benzyl 5,7-dimethoxyquinoline-1(*2H*)-carboxylate (3ca) (Table 1, entry 8). Prepared from **1ca** (0.11 g, 0.33 mmol), *p*-TsOH (62.8 g, 0.33 mmol), BQ (35.7 mg, 0.33 mmol) and $PdCl_2(CH_3CN)_2$ (8.6 mg, 0.033 mmol) in dioxane (22.0 mL). The reaction mixture was stirred for 3 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **3ca** was obtained as an oil (71.5 mg, 67 %): ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.80 (s, 3H), 4.37 (d, J = 4.2 Hz, 2H), 5.24 (s, 2H), 5.78-5.89 (m, 1H), 6.23 (d, J = 1.9 Hz, 1H), 6.73-6.85 (m, 2H), 7.28-7.44 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 43.2, 55.3, 55.6, 67.8, 95.1, 100.7, 111.2, 120.7, 120.8, 128.2, 128.3, 128.6, 136.1, 138.1, 154.0, 155.6, 159.3 ppm; IR (ATR): 1702 cm^{-1}; MS (ESI) *m/z* (rel intensity): 348.1 (MNa^+, 100), 327.1 ($MH^+ + 1$, 9), 326.1 (MH^+, 54), 282.1 (38); HRMS (ESI-TOF): calcd. for $C_{19}H_{19}NO_4Na$: 348.1212 [MNa^+]; found: 348.1215.

1-[5,7-Dimethoxyquinolin-1(2*H*)-yl]ethan-1-one (3da) (Table 1, entry 10). Prepared from **1da** (93.3 mg, 0.40 mmol), *p*-TsOH (75.4 mg, 0.40 mmol), BQ (42.9 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.3 mg, 0.040 mmol) in dioxane (26.4 mL). The reaction mixture was stirred for 1 h at 70 ºC and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **3da** was obtained as an oil (78.2 mg, 85 %): ^1H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.29-4.41 (m, 2H), 5.88 (dt, J = 9.5, 4.2 Hz, 1H), 6.28 (d, J = 2.2 Hz, 1H), 6.36 (br s, 1H), 6.75 (dt, J = 9.5, 1.8 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 22.9, 41.4, 55.5, 55.7, 95.2, 102.0, 112.1, 120.8, 123.1, 138.8, 155.8, 159.2, 170.1 ppm; IR (ATR): 1659 cm^{-1}; MS (ESI) *m/z* (rel intensity):

256.1 (MNa^+, 83), 234.1 (MH^+, 100), 192.1 (8); HRMS (ESI-TOF): calcd. for $C_{13}H_{16}NO_3$: 234.1130 [MH^+]; found: 234.1133. In this reaction, 1-(4,6-dimethoxy-3-methyl-1*H*-indol-1-yl)ethan-1-one **(4da)** was obtained as a by product (solid, 9.5 mg, 10 %): mp (CH_2Cl_2): 141-143 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (d, J = 1.3 Hz, 3H), 2.55 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.35 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 1.3 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 12.4, 24.1, 55.3, 55.8, 92.9, 95.2, 114.7, 118.9, 119.5, 137.9, 154.7, 159.5, 168.7 ppm; IR (ATR): 1685 cm^{-1}; MS (ESI) *m/z* (rel intensity): 234.1 (MH^+, 100), 192.1 (45); HRMS (ESI-TOF): calcd. for $C_{13}H_{16}NO_3$: 234.1130 [MH^+]; found: 234.1138.

5,7-Dimethoxy-1-tosyl-1,2-dihydroquinoline (3fa) (Table 4, entry 1). Prepared from **1fa** (0.11 g, 0.31 mmol), *p*-TsOH (58.4 g, 0.31 mmol), BQ (33.2 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (4.0 mg, 0.015 mmol) in dioxane (20.5 mL). The reaction mixture was stirred for 16 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **3fa** was obtained as an oil (92.5 mg, 87 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.74 (s, 3H), 3.85 (s, 3H), 4.37 (dd, J = 4.3, 1.6 Hz, 2H), 5.40 (dt, J = 9.6, 4.3 Hz, 1H), 6.22-6.36 (m, 2H), 6.93 (d, J = 2.3 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 21.5, 45.2, 55.6, 96.9, 102.9, 112.5, 119.0, 120.4, 127.3, 129.1, 136.6, 136.9, 143.4, 155.7, 159.6 ppm; IR (ATR): 1350 1160 cm^{-1}; MS (ESI) *m/z* (rel intensity): 368.1 (MNa^+, 100), 346.1 (MH^+, 89), 191.1 (33), 190.1 (48); HRMS (ESI-TOF): calcd. for $C_{18}H_{19}NO_4SNa$: 368.0933 [MNa^+]; found, 368.0934.

5,7-Dimethoxy-4-methyl-1-tosyl-1,2-dihydroquinoline (3fb) (Table 4, entry 2). Prepared from **1fb** (0.10 g, 0.28 mmol), *p*-TsOH (54.2 g, 0.28 mmol), BQ (30.8 mg, 0.28 mmol) and $PdCl_2(CH_3CN)_2$ (3.7 mg, 0.014 mmol) in dioxane (19.0 mL). The reaction mixture was stirred for 16 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **3fb** was obtained as an oil (65.5 mg, 64 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 3H), 2.33 (s, 3H), 3.72 (s, 3H), 3.86 (s, 3H), 4.10-4.22 (m, 2H), 5.03-5.14 (m, 1H), 6.33-6.40 (m, 1H), 6.90-6.97 (m, 1H), 7.05-7.14 (m, 2H), 7.30-7.38 (m, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 21.0, 21.4, 45.2,

55.5, 55.6, 98.3, 103.6, 115.0, 118.3, 127.5, 128.9, 132.2, 136.7 ($C_{1'}$), 138.3, 143.1, 157.5, 159.2 ppm; IR (ATR): 1347, 1159 cm^{-1}; MS (ESI) *m/z* (rel intensity): 382.1 (MNa^+, 43), 360.1 (MH^+, 100), 204.1 (10); HRMS (ESI-TOF): calcd. for $C_{19}H_{22}NO_4S$: 360.1270 [MH^+]; found: 360.1272. In this reaction, 5,7-dimethoxy-4-methyl-1-tosyl-1,4-dihydroquinoline (**5fb**) was obtained as a by product (solid, 26.6 mg, 26 %): mp (CH_2Cl_2) 106-108 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 0.39 (d, J = 6.8 Hz, 3H), 2.34 (s, 3H), 3.35 (q, J = 6.8 Hz, 1H), 3.72 (s, 3H), 3.84 (s, 3H), 5.42 (dd, J = 7.5, 6.0 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 7.14-7.24 (m, 3H), 7.53 (d, J = 8.3 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 21.5, 22.7, 26.4, 55.4, 55.6, 96.7, 99.3, 115.5, 120.7, 125.1, 127.6, 129.2, 134.3, 135.9, 143.9, 157.1, 158.7 ppm; IR (ATR): 1350, 1164 cm^{-1}; MS (ESI) *m/z* (rel intensity): 382.1 (MNa^+, 20), 360.1 (MH^+, 100),190.1 (20); HRMS (ESI-TOF): calcd. for $C_{19}H_{22}NO_4S$: 360.1270 [MH^+]; found, 360.1269.

Synthesis of indoles 4. General procedure. To a solution of the corresponding ester **1am-aq, 1bm** (1 mmol) in 1,4-dioxane (66.7 mL), *p*-TsOH (1 mmol), BQ (1 mmol) and $PdCl_2(CH_3CN)_2$ (0.1 mmol) were added and the reaction mixture was stirred at 70 ºC for 4.5 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) affording the corresponding 3-substituted indoles **4am-aq, 4bm.**

Methyl 4,6-dimethoxy-3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (4am) (Table 3, entry 1). Prepared from **1am** (90.7 mg, 0.29 mmol), *p*-TsOH (55.8 mg, 0.29 mmol), BQ (31.7 mg, 0.29 mmol) and $PdCl_2(CH_3CN)_2$ (7.6 mg, 0.029 mmol) in dioxane (19.4 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **4am** was obtained as a solid (61.1 mg, 68 %): mp (CH_2Cl_2): 98-101 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 3H), 3.80 (d, J = 0.9 Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 3.98 (s, 3H), 6.30 (d, J = 2.0, 1H), 7.28 (br s, 1H), 7.37 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 32.3, 51.9, 53.6, 55.2, 55.7, 91.6, 94.7, 113.7, 114.1, 121.1, 137.5,

151.4, 154.3, 159.3, 172.2 ppm; IR (ATR): 1728 cm^{-1} MS (ESI) *m/z* (rel intensity): 308.1 (MH^+, 100), 248.1 (2); HRMS (ESI-TOF): calcd. for $C_{15}H_{18}NO_6$: 308.1134 [MH^+]; found, 308.1136.

***tert*-Butyl 4,6-dimethoxy-3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (4bm)** (Table 3, entry 2). Prepared from **1bm** (0.11 g, 0.33 mmol), *p*-TsOH (62.0 mg, 0.33 mmol), BQ (38.8 mg, 0.33 mmol) and $PdCl_2(CH_3CN)_2$ (8.5 mg, 0.033 mmol) in dioxane (21.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **4bm** was obtained as a solid (46.4 mg, 41 %): mp (CH_2Cl_2): 103-105 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (s, 9H), 3.71 (s, 3H), 3.80 (s, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 6.29 (d, J = 1.7, 1H), 7.26 (br s, 1H), 7.35 (s, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 28.2, 32.4, 51.9, 55.2, 55.7, 83.3, 91.6, 94.5, 113.2, 113.8, 121.7, 137.4, 149.7, 154.2, 159.1, 172.4 ppm; IR (ATR): 1756, 1720 cm^{-1}; MS (ESI) *m/z* (rel intensity): 350.2 (MH^+, 100), 294.1 (72); HRMS (ESI-TOF):calcd. for $C_{18}H_{24}NO_6$: 350.1604 [MH^+]; found, 350.1606.

Methyl 3-(2-ethoxy-2-oxoethyl)-4,6-dimethoxy-1*H*-indole-1-carboxylate (4an) (Table 3, entry 3). Prepared from **1an** (0.13 g, 0.39), *p*-TsOH (75.1 mg, 0.39 mmol), BQ (42.7 mg, 0.39 mmol) and $PdCl_2(CH_3CN)_2$ (10.2 mg, 0.039 mmol) in dioxane (26.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **4an** was obtained as a solid (86.4 mg, 68 %): mp (CH_2Cl_2): 77-80 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 3H), 3.78 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 3.97 (s, 3H), 4.17 (q, J = 7.1 Hz, 2H), 6.30 (d, J = 1.9, 1H), 7.28 (br s, 1H), 7.37 (s, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 14.3, 32.6, 53.6, 55.2, 55.7, 60.6, 91.5, 94.6, 113.8, 114.3, 121.1, 137.5, 151.5, 154.3, 159.3, 171.7 ppm; IR (ATR): 1731 cm^{-1}; MS (ESI) *m/z* (rel intensity): 322.1 (MH^+, 100), 248.1 (3); HRMS (ESI-TOF): calcd. for $C_{16}H_{20}NO_6$: 322.1291 [MH^+]; found: 322.1300.

Methyl 3-(2-buthoxy-2-oxoethyl)-4,6-dimethoxy-1*H*-indole-1-carboxylate (4ao) (Table 3, entry 4). Prepared from **1ao** (0.11 g, 0.31), *p*-TsOH (58.6 mg, 0.31 mmol), BQ (33.3 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (8.0 mg, 0.031 mmol) in dioxane (20.5 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **4ao** was obtained as a solid (68.0 mg, 63 %): mp (CH_2Cl_2): 79-80 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J = 7.3 Hz, 3H), 1.22-1.46 (m,

2H), 1.51-1.69 (m, 2H), 3.79 (s, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 3.99 (s, 3H), 4.17 (t , J = 6.7 Hz, 2H), 6.30 (d, J = 2.0, 1H), 7.29 (br s, 1H), 7.38 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 13.7, 19.1, 30.7, 32.6, 53.6, 55.2, 55.7, 64.5, 91.5, 94.6, 113.8, 114.3, 121.1, 137.5, 151.5, 154.3, 159.3, 171.8 ppm; IR (ATR): 1731 cm^{-1}; MS (ESI) *m/z* (rel intensity): 350.2 (MH^+, 100), 349.2 (5); HRMS (ESI-TOF): calcd. for $C_{18}H_{24}NO_6$: 350.1604 [MH^+]; found, 350.1604.

Methyl 3-[2-(*tert*-butoxy)-2-oxoethyl]-4,6-dimethoxy-1*H*-indole-1-carboxylate (4ap) (Table 3, entry 5). Prepared from **1ap** (0.14 g, 0.40), *p*-TsOH (75.9 mg, 0.40 mmol), BQ (43.2 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.4 mg, 0.040 mmol) in dioxane (26.6 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **4ap** was obtained as a solid (75.3 mg, 54 %): ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.70 (s, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 3.98 (s, 3H), 6.30 (d, J = 2.0, 1H), 7.27 (br s, 1H), 7.37 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 28.3, 33.6, 53.6, 55.1, 55.7, 80.3, 91.5, 94.6, 113.9, 114.8, 121.0, 137.5, 151.5, 154.3, 159.2, 171.0 ppm; IR (ATR): 1735 cm^{-1}; MS (ESI) *m/z* (rel intensity): 350.2 (MH^+, 31), 294.1 (100); MS (ESI) *m/z* (rel intensity): calcd. for $C_{18}H_{24}NO_6$: 350.1604 [MH^+]; found, 350.1608.

Methyl 3-[2-(benzyloxy)-2-oxoethyl]-4,6-dimethoxy-1*H*-indole-1-carboxylate (4aq) (Table 3, entry 6). Prepared from **1aq** (0.10 g, 0.27), *p*-TsOH (51.2 mg, 0.27 mmol), BQ (29.1 mg, 0.27 mmol) and $PdCl_2(CH_3CN)_2$ (7.0 mg, 0.027 mmol) in dioxane (17.9 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **4aq** was obtained as a solid (80.4 mg, 78 %): mp (CH_2Cl_2): 136-138 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 3H), 3.85 (s, 2H), 3.87 (s, 3H), 3.99 (s, 3H), 5.17 (s, 2H), 6.28 (d, J = 1.9, 1H), 7.24-7.45 (m, 7H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 32.6, 53.6, 55.0, 55.7, 66.4, 91.5, 94.7, 113.8, 114.1, 121.2, 128.1, 128.3, 128.5, 136.2, 137.5, 151.5, 154.3, 159.3, 171.5 ppm; IR (ATR): 1735 cm^{-1}; MS (ESI) *m/z* (rel intensity): 406.1 (MNa^+ + 1, 81), 384.1 (MH^+, 100), 383.1 (17); HRMS (ESI-TOF): calcd. for $C_{21}H_{22}NO_6$: 384.1447 [MH^+]; found, 384.1452.

Synthesis of 1,4-dihydroquinolines 5. General procedure. To a solution of the corresponding *N*-ptotected (3,5-dimethoxyphenyl)allyl aniline **1** (1 mmol) in 1,4-dioxane (66.7 mL), *p*-TsOH (1 mmol),

BQ (1 mmol) and $PdCl_2(CH_3CN)_2$ (0.05 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) affording the corresponding 1,4-dihydroquinolines **5.**

Methyl 5,7-dimethoxy-4-methylquinoline-1(*4H*)-carboxylate (5ab) (Table 2). Prepared from **1ab** (0.11 g, 0.42 mmol), *p*-TsOH (79.8 mg, 0.42 mmol), BQ (45.4 mg, 0.42 mmol) and $PdCl_2(CH_3CN)_2$ (5.4 mg, 0.021 mmol) in dioxane (28 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **5ab** was obtained as an oil (62.6 mg, 57 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (d, J = 6.8 Hz, 3H), 3.53-3.70 (m, 1H), 3.80 (s, 3H), 3.86 (s, 6H), 5.28-5,44 (m, 1H), 6.30 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 22.1, 26.1, 53.2, 55.4, 55.5, 95.5, 98.1, 114.6, 116.0, 125.1, 137.3, 153.2, 156.8, 158.4 ppm; IR (ATR): 1705 cm^{-1}; MS (EI) *m/z* (rel intensity): 263.1 (M^+, 10), 248.2 (100), 189.1 (64); HRMS (ESI-TOF): calcd. for $C_{14}H_{18}NO_4$: 264.1236 [MH^+]; found, 264.1251.

Methyl 5,7-dimethoxy-4-phenylquinoline-1(*4H*)-carboxylate (5ac) (Table 2). Prepared from **1ac** (98.8 mg, 0.30 mmol), *p*- TsOH (57.4 mg, 0.30 mmol), BQ (32.6 mg, 0.30 mmol) and $PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) in dioxane (20.1 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5ac** was obtained as a solid (76.0 mg, 77 %): mp (CH_2Cl_2) 137-140 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.82 (d, J = 6.0 Hz, 1H), 5.42-5.55 (m, 1H), 6.29 (br s, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.11-7.28 (m, 5H), 7.43 (br s, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 37.3, 53.4, 55.4, 55.6, 95.8, 97.9, 112.1, 113.9, 125.2, 126.2, 127.4, 128.4, 137.5, 144.8, 153.2, 157.2, 159.0 ppm; IR (ATR): 1727 cm^{-1}; MS (EI) *m/z* (rel intensity): 325.1 (M^+, 20), 248.1 (100), 189.1 (19); HRMS (ESI-TOF): calcd. for $C_{19}H_{20}NO_4$: 326.1392 [MH^+]; found: 326.1400.

***tert*-Butyl 5,7-dimethoxy-4-phenylquinoline-1(*4H*)-carboxylate (5bc)** (Table 2). Prepared from **1bc** (0.11 g, 0.29 mmol), *p*- TsOH (55.3 mg, 0.29 mmol), BQ (31.4 mg, 0.29 mmol) and $PdCl_2(CH_3CN)_2$ (3.8 mg, 0.015 mmol) in dioxane (19.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **5bc** was obtained as a solid (77.4 mg, 73 %): mp (CH_2Cl_2) 110-112 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (s, 9H), 3.71 (s, 3H), 3.84 (s, 3H), 4.83 (d, J = 6.2 Hz, 1H), 5.45 (dd, J = 7.7, 6.2 Hz, 1H), 6.28 (d, J = 2.3 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 7.11-7.28 (m, 5H), 7.37 (d, J = 2.3 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 28.4, 37.4, 55.4, 55.6, 82.2, 95.5, 98.4, 112.4, 113.2, 126.0, 126.1, 127.5, 128.4, 137.9, 145.1, 151.6, 157.1, 158.9 ppm; IR (ATR): 1727 cm^{-1}; MS (EI) *m/z* (rel intensity): 390.2 (MNa^+, 27), 312.1 (100); HRMS (ESI-TOF): calcd. for: $C_{22}H_{25}NO_4Na$: 390.1681 [MNa^+]; found: 390.1684.

Methyl 5,7-dimethoxy-4-(*p*-tolyl)quinoline-1(*4H*)-carboxylate (5ad) (Table 2). Prepared from **1ad** (0.12 g, 0.36 mmol), *p*-TsOH (67.8 mg, 0.36 mmol), BQ (38.5 mg, 0.36 mmol) and $PdCl_2(CH_3CN)_2$ (4.6 mg, 0.018 mmol) in dioxane (23.8 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5ad** was obtained as a solid (98.7 mg, 82 %): mp (CH_2Cl_2) 105-106 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.71 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.79 (d, J = 6.2 Hz, 1H), 5.48 (dd, J = 7.7, 6.2 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 6.98-7.13 (m, 5H), 7.42 (d, J = 2.3 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 21.0, 36.8, 53.3, 55.4, 55.6, 95.8, 97.9, 112.3, 114.1, 125.0, 127.3, 129.1, 135.7, 137.5, 141.9, 153.2, 157.2, 158.9 ppm; IR (ATR): 1727 cm^{-1}; MS (ESI) *m/z* (rel intensity): 340.2 (MH^+, 100), 248.1 (3); HRMS (ESI-TOF): calcd. for $C_{20}H_{22}NO_4$: 340.1549 [MH^+]; found: 340.1553.

Methyl 5,7-dimethoxy-4-(*m*-tolyl)quinoline-1(4*H*)-carboxylate (5ae) (Table 2). Prepared from **1ae** (0.11 g, 0.31 mmol), *p*-TsOH (59.0 mg, 0.31 mmol), BQ (33.5 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (4.0 mg, 0.016 mmol) in dioxane (20.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5ae** was obtained as a solid (96.5 mg, 92 %): mp (CH_2Cl_2) 101-102 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.71 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.79 (d, J = 6.2 Hz, 1H), 5.48 (m, 1H), 6.30 (d, J = 2.1 Hz, 1H), 6.91-7.18 (m, 5H), 7.43 (d, J =

2.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 21.5, 37.2, 53.3, 55.4, 55.6, 95.8, 97.9, 112.1, 114.0, 124.4, 125.0, 127.0, 128.1, 128.3, 137.6, 137.9, 144.8, 153.2, 157.3, 159.0 ppm; IR (ATR): 1727 cm^{-1}; MS (ESI) *m/z* (rel intensity): 340.2 (MH^+, 100), 248.1 (2); HRMS (ESI-TOF): calcd. for $C_{20}H_{22}NO_4$: 340.1549 [MH^+]; found: 340.1555.

Methyl 5,7-dimethoxy-4-(*o*-tolyl)quinoline-1(4*H*)-carboxylate (5af) (Table 2). Prepared from **1af** (0.11 g, 0.31 mmol), *p*-TsOH (59.6 mg, 0.31 mmol), BQ (33.8 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (4.1 mg, 0.016 mmol) in dioxane (20.9 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5af** was obtained as a solid (87.6 mg, 82 %): mp (CH_2Cl_2) 118-121 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H), 3.63 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 5.01 (d, J = 5.9 Hz, 1H), 5.43 (m, 1H), 6.29 (d, J = 2.3 Hz, 1H), 6.77-7.17 (m, 5H), 7.50 (d, J = 2.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 17.3, 34.0, 53.3, 55.4, 55.7, 95.8, 97.8, 112.1, 112.5, 124.6, 126.0, 126.6, 127.5, 129.9, 134.6, 138.1, 143.6, 153.2, 157.3, 159.0 ppm; IR (ATR): 1724 cm^{-1}; MS (ESI) *m/z* (rel intensity): 340.2 (MH^+, 100), 248.1 (2); HRMS (ESI-TOF): calcd. for $C_{20}H_{22}NO_4$: 340.1549 [MH^+]; found, 340.1557.

Methyl 5,7-dimethoxy-4-(4-methoxyphenyl)quinoline-1(*4H*)-carboxylate (5ag) (Table 2). Prepared from **1ag** (0.13 g, 0.37 mmol), *p*-TsOH (69.7 mg, 0.37 mmol), BQ (39.6 mg, 0.37 mmol) and $PdCl_2(CH_3CN)_2$ (4.8 mg, 0.018 mmol) in dioxane (24.4 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5ag** was obtained as a solid (98.7 mg, 82 %): mp (CH_2Cl_2) 109-110 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.75 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 4.77 (d, J = 6.2 Hz, 1H), 5.47 (dd, J = 7.7, 6.2 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 6.78 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 7.7 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 2.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 36.4, 53.3, 55.2, 55.4, 55.6, 95.8, 98.0, 112.5, 113.8, 114.2, 125.0, 128.4, 137.1, 137.4, 153.2, 157.1, 158.0, 158.9 ppm; IR (ATR): 1727 cm^{-1}; MS (ESI) *m/z* (rel intensity): 378.1 (MNa^+, 100), 356.2 (MH^+, 99), 248.1 (16); HRMS (ESI-TOF): calcd. for $C_{20}H_{21}NO_5Na$: 378.1317 [MNa^+]; found: 378.1324.

Methyl 5,7-dimethoxy-4-(3-methoxyphenyl)quinoline-1(4*H*)-carboxylate (5ah) (Table 2). Prepared from **1ah** (57.6 mg, 0.16 mmol), *p*-TsOH (30.7 mg, 0.16 mmol), BQ (17.4 mg, 0.16 mmol) and $PdCl_2(CH_3CN)_2$ (2.1 mg, 0.008 mmol) in dioxane (10.8 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5ah** was obtained as a solid (46.1 mg, 81 %): mp (CH_2Cl_2) 101-103 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.74 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 4.80 (d, J = 6.2 Hz, 1H), 5.38-5.54 (m, 1H), 6.29 (d, J = 1.8 Hz, 1H), 6.65-7.18 (m, 5H), 7.41 (d, J = 2.1 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 37.2, 53.3, 55.0, 55.4, 55.6, 95.8, 98.0, 111.3, 112.0, 113.3, 113.8, 119.8, 125.3, 129.3, 137.5, 146.4, 153.1, 157.2, 159.0, 159.6 ppm; IR (ATR): 1720 cm^{-1}; MS (ESI) *m/z* (rel intensity): 356.2 (MH^+, 100), 248.1 (1); MS (ESI) *m/z* (rel intensity): calcd. for $C_{20}H_{22}NO_5$: 356.1498 [MH^+]; found, 356.1510.

Methyl 4-[(1,1´-biphenyl)-4-yl]-5,7-dimethoxyquinoline-1(*4H*)-carboxylate (5ai) (Table 2). Prepared from **1ai** (0.11 g, 0.28 mmol), *p*- TsOH (53.9 mg, 0.28 mmol), BQ (30.7 mg, 0.28 mmol) and $PdCl_2(CH_3CN)_2$ (3.7 mg, 0.014 mmol) in dioxane (18.9 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5ai** was obtained as a solid (82.6 mg, 73 %): mp (CH_2Cl_2) 54-56 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.89 (d, J = 6.2 Hz, 1H), 5.53 (dd, J = 7.7, 6.2 Hz, 1H), 6.33 (d, J = 2.3 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 7.20-7.71 (m, 10H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 36.9, 53.4, 55.4, 55.6, 95.8, 98.0, 112.0, 113.8, 125.4, 127.0, 127.1, 127.2, 127.8, 128.7, 137.5, 139.1, 141.1, 143.9, 153.2, 157.2, 159.1 ppm; IR (ATR): 1724 cm^{-1}; MS (ESI) *m/z* (rel intensity):402.2 (MH^+, 100), 248.1 (1); HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}NO_4$: 402.1705 [MH^+]; found, 402.1710.

Methyl 4-[4-(*tert*-butyl)phenyl]-5,7-dimethoxyquinoline-1(*4H*)-carboxylate (5aj) (Table 2). Prepared from **1aj** (91.5 mg, 0.24 mmol), *p*-TsOH (45.4 mg, 0.24 mmol), BQ (25.8 mg, 0.24 mmol) and $PdCl_2(CH_3CN)_2$ (3.1 mg, 0.012 mmol) in dioxane (15.9 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **5aj** was obtained as a solid (79.1 mg, 87 %): mp (CH_2Cl_2) 107-109 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 9H), 3.73 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H), 4.82 (d, J = 6.3 Hz, 1H), 5.51 (dd, J = 7.6, 6.3 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 7.08 (d, J

= 7.7 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 2.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 31.4, 34.3, 36.6, 53.3, 55.4, 55.6, 95.8, 98.0, 112.6, 114.2, 125.3, 127.0, 137.5, 141.6, 148.8, 153.2, 157.1, 158.9 ppm; IR (ATR): 1724 cm^{-1}; MS (ESI) *m/z* (rel intensity): 382.2 (MH^+, 100), 248.1 (10); HRMS (ESI-TOF): calcd. for $C_{23}H_{28}NO_4$: 382.2018 [MH^+]; found, 382.2019.

Methyl 5,7-dimethoxy-4-(4-fluorophenyl)quinoline-1(4*H*)-carboxylate (5ak) (Table 2). Prepared from **1ak** (0.11 mg, 0.31 mmol), *p*-TsOH (59.9 mg, 0.31 mmol), *p*-BQ (34.0 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (4.1 mg, 0.016 mmol) in dioxane (21.0 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5ak** was obtained as a solid (77.5 mg, 72 %): mp (CH_2Cl_2) 129-131 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 4.82 (d, *J* = 6.2 Hz, 1H), 5.47 (dd, *J* = 7.7, 6.2 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 6.88-6.97 (m, 2H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.14-7.21 (m, 2H), 7.45 (d, *J* = 2.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 36.5, 53.4, 55.4, 55.6, 95.8, 98.0, 112.0, 113.6, 115.0 (d, *J* = 21.3 Hz), 125.3, 128.9 (d, *J* = 8.0 Hz), 137.4, 140.6 (d, *J* = 3.1 Hz), 153.1, 157.1, 159.1, 161.4 (d, *J* = 243.9 Hz) ppm; IR (ATR): 1724 cm^{-1}; MS (ESI) *m/z* (rel intensity): 344.1 (MH^+, 100), 301.1 (1); HRMS (ESI-TOF): calcd. for $C_{19}H_{19}FNO_4$: 344.1298 [MH^+]; found: 344.1311.

Methyl 5,7-dimethoxy-4-(naphthalene-1-yl)quinoline-1(*4H*)-carboxylate (5al) (Table 2). Prepared from **1al** (72.0 mg, 0.19 mmol), *p*-TsOH (36.3 mg, 0.19 mmol), BQ (20.6 mg, 0.19 mmol) and $PdCl_2(CH_3CN)_2$ (2.5 mg, 0.010 mmol) in dioxane (12.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **5al** was obtained as a solid (58.4 mg, 82 %): mp (CH_2Cl_2) 140-142 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 5.61-5.71 (m, 2H), 6.33 (d, *J* = 2.4 Hz, 1H), 6.92-7.00 (m, 2H), 7.27-7.34 (m, 1H), 7.47-7.55 (m, 2H), 7.56-7.64 (m, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.84-7.91 (m, 1H); 8.34 (d, *J* = 8.4 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 33.3, 53.3, 55.5, 55.6, 95.9, 97.9, 111.5, 113.0, 123.4, 124.1, 125.0, 125.4, 125.9, 126.1, 126.6, 128.9, 130.9, 134.0, 138.7, 141.2, 153.2, 157.3, 159.3 ppm; IR (ATR): 1727 cm^{-1}; MS (ESI) *m/z* (rel intensity): 398.1 (MNa^+, 53), 376.2 (MH^+, 100), 248.1 (25); HRMS (ESI-TOF): calcd. for $C_{23}H_{22}NO_4$: 376.1549 [MH^+]; found: 376.1553.

5,7-Dimethoxy-4-phenyl-1-tosyl-1,4-dihydroquinoline (5fc) (Table 4, entry 3). Prepared from **1fc** (0.10 g, 0.25 mmol), *p*- TsOH (46.6 mg, 0.25 mmol), BQ (26.5 mg, 0.25 mmol) and $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.012 mmol) in dioxane (16.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/CH_2Cl_2 4/6), **5fc** was obtained as a solid (43.6 mg, 42 %): mp (CH_2Cl_2) 161-163 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.55 (s, 3H), 3.86 (s, 3H), 4.64 (d, J = 5.6 Hz, 1H), 5.35-5.50 (m, 1H), 6.24 (br s, 1H), 6.44-6.53 (m, 2H), 6.89-6.98 (m, 3H), 6.99-7.08 (m, 1H), 7.18 (d, J = 7.9 Hz, 2H), 7.42 (br s, 1H) 7.63 (d, J = 7.9 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 21.6, 37.7, 55.4, 55.5, 96.5, 97.6, 111.2, 115.7, 124.1, 125.5, 127.2, 127.6, 127.8, 129.7, 134.7, 136.1, 144.2, 144.9, 157.9, 159.4 ppm; IR (ATR): 1350, 1154 cm^{-1}; MS (ESI) *m/z* (rel intensity): 422.1 (MH^+, 100), 344.1 (3), 267.1 (5). 266.1 (8); HRMS (ESI): *m/z* calcd. for $C_{24}H_{24}NO_4S$: 422.1426 [MH^+]; found: 422.1431.

4-Benzyl-5,7-dimethoxy-1-tosyl-1,4-dihydroquinoline (5fd) (Table 4, entry 4). Prepared from **1fd** (0.10 g, 0.24 mmol), *p*-TsOH (44.8 mg, 0.24 mmol), BQ (25.4 mg, 0.24 mmol) and $PdCl_2(CH_3CN)_2$ (3.1 mg, 0.012 mmol) in dioxane (15.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **5fd** was obtained as an oil (61.9 mg, 60 %): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97-1.13 (m, 1H), 2.34 (s, 3H), 2.44-2.57 (m, 1H), 3.51-3.61 (m, 1H), 3.71 (s, 3H), 3.87 (s, 3H), 5.24 (t, J = 6.7 Hz, 1H), 6.33 (br s, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 2H), 7.13-7.33 (m, 6H), 7.64 (d, J = 7.5 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 21.6, 33.8, 44.7, 55.5, 55.6, 96.7, 99.4, 114.2, 118.8, 125.7, 126.0, 127.7, 128.1, 128.9, 129.5, 134.6, 136.3, 139.7, 144.3, 157.1, 159.0 ppm; IR (ATR): 1358, 1168 cm^{-1}; MS (ESI) *m/z* (rel intensity): 458.1 (MNa^+, 100), 436.2 (MH^+, 91), 345.1 (15), 344.1 (96); HRMS (ESI-TOF): *m/z* calcd. for $C_{25}H_{25}NO_4SNa$: 458.1402 [MNa^+]; found, 458.1406.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 5,7-dimethoxy-4-methylquinoline-1(4*H*)-carboxylate (5gb) (Scheme 6). Prepared from **1gb** (0.11 g, 0.28 mmol), *p*-TsOH (52.5 mg, 0.28 mmol), BQ (29.8 mg, 0.28 mmol) and $PdCl_2(CH_3CN)_2$ (3.6 mg, 0.014 mmol) in dioxane (18.4 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 18/1), **5gb** was

obtained as a mixture of C-4 diastereoisomers in a 58:42 ratio and as an oil (71.3 mg, 67 %): $[\alpha]_D^{20}$ = -57.9 (c 1.13, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79-0.97 (m, 10H, both isom), 1.04-1.18 (m, 5H, both isom), 1.44-1.61 (m, 2H, both isom), 1.69-1.76 (m, 2H, both isom), 1.93-2.04 (m, 1H, both isom), 2.14-2.23 (m, 1H, both isom), 3.60-3.68 (m, 1H, both isom), 3.80 (s, 3H, both isom), 3.81 (s, 3H, both isom), 4.68-4.78 (m, 1H, both isom), 5.33-5.38 (m, 1H, both isom), 6.30 (d, J = 2.3 Hz, 1H, both isom), 6.93 (d, J = 7.3 Hz, 1H, minor isom)6.95 (d, J = 7.3 Hz, 1H major isom), 7.32 (d, J = 2.3 Hz, 1H, minor isom), 7.35 (d, J = 2.3 Hz, 1H, major isom); ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ (major isom.): 16.6, 20.8, 22.0, 22.1, 23.7, 26.1, 26.5, 31.5, 34.3, 41.2, 47.3, 55.4, 55.5, 76.7, 95.5, 98.1, 114.5, 115.5, 125.2, 137.5, 152.5, 156.8, 158.4 ppm (minor isom.): 16.6, 20.8, 22.1, 22.2, 23.7, 26.1, 26.7, 31.5, 34.3, 41.4, 47.3, 55.4, 55.5, 76.5, 95.6, 98.0, 114.8, 115.8, 125.3, 137.6, 152.5, 156.8, 158.4 ppm; IR (ATR): 1716 cm^{-1};MS (ESI) *m/z* (rel intensity):, 410.2 (MNa^+, 82), 250.1 (9); HRMS (ESI-TOF): calcd. for $C_{23}H_{33}NO_4Na$: 410.2307 [MNa^+]; found: 410.2316.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 5,7-dimethoxy-4-phenylquinoline-1(4*H*)-carboxylate (5gc) (Scheme 6). Prepared from **1gc** (0.12 g, 0.26 mmol), *p*-TsOH (48.8 mg, 0.26 mmol), BQ (27.7 mg, 0.26 mmol) and $PdCl_2(CH_3CN)_2$ (3.3 mg, 0.013 mmol) in dioxane (17.1 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **5gc** was obtained as a mixture of diastereoisomers in a 63:37 ratio and as an oil (89.4 mg, 78 %): $[\alpha]_D^{20}$ = –25.3 (c 0.88, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72-0.98 (m, 10H, both isom), 1.07-1.18 (m, 2H, both isom), 1.46-1.53 (m, 1H, both isom), 1.53-1.60 (m, 1H. both isom), 1.70-1.76 (m, 2H, both isom), 1.94-2.03 (m, 1H, both isom), 2.18-2.25 (m, 1H, $H_{2'}$), 3.73 (s, 3H minor isom), 3.74 (s, 3H major isom), 3.83 (s, 3H, minor isom), 3.84 (s, 3H, major isom), 4.76-4.89 (m, 2H, both isom), 5.50 (ddd, J = 11.1, 7.6, 6.3 Hz, 1H, both isom), 6.28 (d, J = 2.2 Hz, 1H both isom), 7.08 (d, J = 7.6 Hz, 1H, minor isom),7.09 (d, J = 7.6 Hz, 1Hmajor isom), 7.12-7.25 (m, 5H, both isom), 7.38 (d, J = 2.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ (major isom.): 16.6, 20.8, 22.1, 23.7, 26.6, 31.5, 34.3, 37.3, 41.2, 47.4, 55.4, 55.6, 77.0, 95.7, 98.3, 112.5, 113.8, 125.6, 126.2, 127.4, 128.3, 137.7, 145.0, 152.5, 157.1, 158.9 ppm (minor isom.): 16.5, 20.8, 22.1, 23.6, 26.6, 31.5 ($C_{5'}$), 34.3, 37.3, 41.4, 47.4, 55.4, 55.6, 76.7, 96.0, 98.2, 113.0,

114.2, 125.8, 126.2, 127.5, 128.3, 137.7, 144.8, 152.4, 157.0, 158.9 ppm; IR (ATR): 1716 cm^{-1}; MS (ESI) *m/z* (rel intensity): 474.3 (MNa^+, 100), 363.2 (5); HRMS (ESI): *m/z* calcd. for $C_{28}H_{37}NO_4Na$: 474.2620 [MNa^+]; found: 474.2621.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 5,7-dimethoxy-4-(naphthalene-1-yl)quinolone-1(4*H*)-carboxylate (5gl) (Scheme 6). Prepared from **1gl** (84.8 mg, 0.17 mmol), *p*-TsOH (32.2 mg, 0.17 mmol), BQ (18.3 mg, 0.17 mmol) and $PdCl_2(CH_3CN)_2$ (2.2 mg, 0.0085 mmol) in dioxane (11.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **5gl** was obtained as a mixture of diastereoisomers in a 58:42 ratio and as a solid (66.5 mg, 79 %): mp (CH_2Cl_2) 73-75 ºC; $[\alpha]_D^{20}$ = –87.0 (0.71, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 0.78-0.99 (m, 10H), 1.03-1.27 (m, 2H), 1.41-1.66 (m, 2H), 1.68-1.79 (m, 2H), 1.80-2.07 (m, 1H), 2.17-2.25 (m, 1H), 3.56 (s, 3H), 3.92 (s, 3H), 4.84 (qd, *J* = 10.7, 4.3 Hz, 1H), 5.61-5.77 (m, 2H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.93-7.11 (m, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.49-7.58 (m, 2H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 8.1 Hz), 7.90 (d, *J* = 7.7 Hz, 1H); 8.39 (d, *J* = 8.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ (major isom.): 16.7, 20.8, 22.0, 23.7, 26.6, 31.5, 33.3, 34.3, 41.1, 47.3, 55.5, 55.6, 76.7, 95.8, 98.1, 112.8, 113.4, 123.5, 124.1, 125.3, 125.9, 126.1, 126.6, 128.9, 131.0, 134.0, 138.9, 141.3, 152.5, 157.2, 159.1 ppm (minor isom.): 16.5, 20.7, 22.1, 23.6, 26.4, 31.5, 33.2, 34.3, 41.4, 47.3, 55.5, 55.6, 76.7, 96.0, 98.1, 111.6, 112.1, 123.5, 124.2, 125.3, 125.8, 126.1, 126.5, 128.9, 131.0, 134.0, 138.9, 141.3, 152.6, 157.2, 159.1 ppm; IR (ATR): 1713 cm^{-1}; MS (ESI) *m/z* (rel intensity): 522.3 (MNa^+, 58), 500.3 (MH^+, 28), 362.1 (100); HRMS (ESI-TOF): calcd. for $C_{32}H_{38}NO_4$: 500.2801 [MH^+]; found, 500.2794.

Use of Boc-Val-OH as ligand. Synthesis of 5ac (1 mmol scale) (Table 2). To a solution of **1ac** (0.3328 g, 1 mmol) in 1,4-dioxane (68 mL), *p*-TsOH (0.1934 g, 1 mmol), BQ (0,1081 g, 1 mmol), Boc-Val-OH (0.02208 g, 0.1 mmol) and $PdCl_2(CH_3CN)_2$ (0.019 g, 0.05 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash

column chromatography (silica gel, petroleum ether/AcOEt 8/2) affording **5ac** as a solid (0.2759 g, 85 %).

Methyl (2-allyl-3,5-dimethoxyphenyl)carbamate (6). Over a solution of 2-allyl-3,5-dimethoxyaniline[32] (51.1 mg, 0.26 mmol) and pyridine (42.6 μL, 0.53 mmol) in dry THF (7 mL) under argon atmosphere, methyl chloroformate (22.5 μL, 0.29 mmol) was added dropwise. The reaction was stirred for 16 h at room temperature and afterwards the solvent was removed under reduced pressure. The crude reaction was dissolved in CH_2Cl_2 (15 mL) and washed with a 10% aqueous solution of HCl (2 × 15 mL) and with water (15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/AcOEt 8/2) afforded **6** as a solid (63.9 mg, 96 %): mp (CH_2Cl_2): 83-84 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (dt, J = 5.6, 1.6 Hz, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.93-5.14 (m, 2H), 5.83-5.97 (m, 1H), 5.26 (d, J = 2.4 Hz, 1H), 6.69 (br s, 1H), 7.18 (br s, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 27.9, 52.3, 55.4, 55.8, 95.0, 97.8, 109.2, 115.2, 136.1, 137.9, 154.3, 158.1, 159.4 ppm; IR (ATR): 3310, 1695 cm^{-1}; MS (ESI): *m/z* (%):274.1 (MNa^+, 100), 252.1 (6); HRMS (ESI-TOF): calcd. for $C_{13}H_{17}NO_4Na$: 274.1055 [MNa^+]; found: 274.1060.

Methyl 4,6-dimethoxy-2-methyl-1*H*-indole-1-carboxylate (7). Over a solution of **6** (55.5 mg, 0.22 mmol) in dioxane (14.7 mL), *p*-TsOH (42.0 mg, 0.22 mmol), BQ (23.9 mg, 0.22 mmol) and $PdCl_2(CH_3CN)_2$ (2.9 mg, 0.011 mmol) were added. The solution was stirred at room temperature for 3 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) affording **7** as a solid (42.7 mg, 78 %): mp (CH_2Cl_2): 88-90 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.02 (s, 3H), 6.35 (d, J = 1.9 Hz, 1H), 6.36 (br s, 1H), 7.36 (d, J = 1.9 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 16.8, 53.4, 55.4, 55.8, 92.7, 94.3, 105.1, 113.7, 134.4, 138.0, 152.2, 152.9, 158.2 ppm; IR (ATR): 1720 cm^{-1}; MS (ESI) *m/z* (rel intensity):

250.1 (MH^+, 100), 190.1 (4); HRMS (ESI-TOF): calcd. for $C_{13}H_{16}NO_4$: 250.1079 [MH^+]; found, 250.1079.

Supporting Information Available. Schemes for the preparation of substrates **1**. Additional cyclization assays on **1gc**. Computational data. Copies of ^1H and ^{13}C NMR spectra of compounds **1-7**. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgments. Ministerio de Economía y Competitividad (CTQ2016-74881-P; CTQ2016-78083-P) and Gobierno Vasco (IT1045-16) are gratefully acknowledged for their financial support. A.C.-M. wishes to thank Gobierno Vasco for a grant. Computational, technical and human support provided by Servicios Generales de Investigación SGIker (UPV/EHU, MINECO, GV/EJ, ERDF and ESF) is also acknowledged.

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(26) DFT Calculations were run with the Gaussian 16 suite of programs. See Supporting Information for details.

(27) When the computed energies of the structures in Figures 3 and 4 were compared a stabilizing effect of the coordination of the oxygen to palladium by ca. 2 kcal/mol was noted. See SI for further details.

(28) The diastereomers could not be separated by chromatographic methods and the ratio was stablished by integration of representative signals in the ^{1}H NMR spectrum (for **5gb and 5gc**) or in the ^{13}C NMR (for **5gl**). The diastereoselectivity could not be improved in the presence of MPAA, acids, or changing the palladium precatalyst. See SI for additional assays performed.

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