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Primary Amines as Directing Groups in the Ru-Catalyzed Synthesis of Isoquinolines, Benzoisoquinolines, and Thienopyridines

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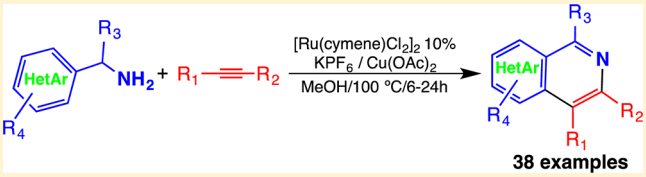
Supporting Information

ABSTRACT: Isoquinolines, benzoisoquinolines, thieno[3,2-*c*]pyridines and fused heteroaryl[2,3-*c*] pyridines, with a wide variety of substituents at different positions of the aromatic or heteroaromatic rings, have been synthesized by Ru-catalyzed oxidative coupling of a broad range of benzylamines or heterocycles with internal alkynes. All benzylamines and heterocycles have unprotected primary amines as efficient directing groups.



INTRODUCTION

The bicyclic isoquinoline core, and its related derivatives containing heterocycle-fused pyridines, are structural motifs almost ubiquitous among natural products and compounds with pharmaceutical and biological activity.[1] For instance, quinisocaine[2] and papaverine,[3] shown in Figure 1, are

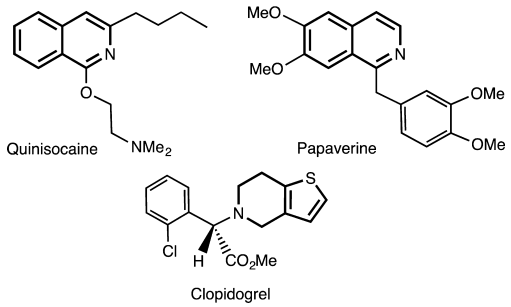


Figure 1. Isoquinolines and thienopyridine derivatives of pharmaceutical importance.

isoquinoline-based commercial drugs, the former being widely used as a topical anesthetic, while the latter is used as vasodilator and antispasmodic. In the same context, the clopidrogel, widely used due to its impressive antithrombotic activity, is based on the thieno[3,2-*c*]pyridine scaffold.[4,5]

Due to their practical importance, diverse synthetic methods for the preparation of isoquinolines[6] and thienopyridines[7] have been developed and reported. Isoquinolines have been traditionally prepared using the Pomeranz–Fritsch,[6a−c] Bischler–Napieralski,[6d,e] and Pictet–Spengler[6f,g] methods, while the Skraup reaction[7a] (also used for the preparation of quinolines) has been the main route for the synthesis of thienopyridines.[7b] In spite of the existence of these well established procedures,[6,7] isoquinolines and thienopyridines (and other heterocycle-fused pyridines) still are specially difficult to synthesize in specific cases. The obtention of isoquinolines is often limited to electron-rich carbocycles,[8] while multistep procedures, low yields, harsh conditions, and a narrow scope of substituents is usually encountered in the design of synthetic routes for the different isomers of thienopyridines and related compounds.[9]

Therefore, the development of alternative preparative pathways using conceptually different routes is still of high interest. The use of transition metals for the activation and functionalization of C−H bonds as a synthetic strategy has gained an increasing interest during the last years due to its versatility, efficiency, selectivity, and tolerance to a wide array of functional groups.[10] One of the most successful metal-mediated methods for the synthesis of *N*-heterocycles is the catalytic dehydrogenative coupling of internal alkynes with (hetero)aryl-based substrates, directed through ortho-metalation, where the directing group in the aryl or heteroaryl moiety usually carries the N atom which is finally incorporated to the *N*-heterocycle. Impressive recent work in this area has been performed by Ackermann, Fagnou, and others, mostly involving aryl precursors. As a result, isoquinolines, isoquinolinium salts, isoquinolinones, pyridines, pyridones, or indoles, have been obtained.[11,12] In contrast, the synthesis of thienopyridines or other fused bis-heterocycles using the same strategy is scarcely developed and few examples have been reported.[12]

In addition to this synthetic limitation, the reported cases show other methodological restrictions (eq 1 in Scheme 1), since the functional group containing the N-atom has to be an imine, an oxime, or a C═N double bond formed "in situ" by reaction of a keto-precursor with an amine or a related derivative (for instance, hydroxylamine). Even when arylamides or heteroarylamides are used as precursors (eq 2, Scheme 1), the N atom has to be at least partially substituted. This means that not all N-containing functional groups are allowed for the promotion of the coupling and that the N atom in the

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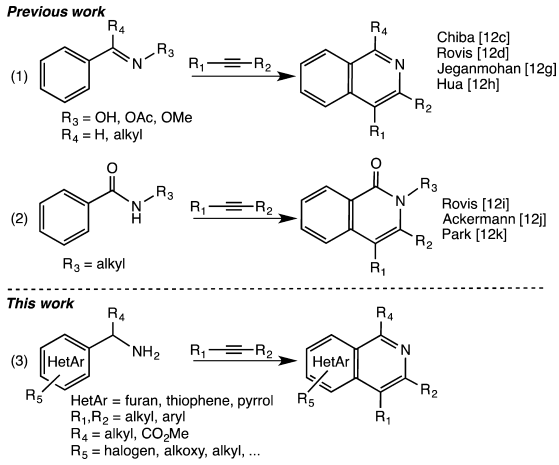
Scheme 1. Most Remarkable Previous Work Performed in the Synthesis of Isoquinolines and Related Derivatives and Comparison with This Contribution



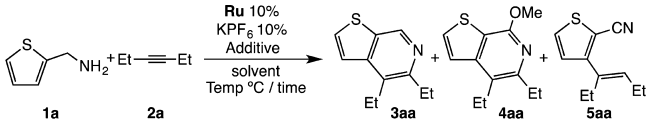
precursors must be protected. It is clear that this mandatory N-protection introduces additional steps into the whole synthetic sequence of a target compound, making it longer in comparison with those using unprotected precursors. Moreover, most of these processes are catalyzed by expensive Rh(III) derivatives,[12c−f,i,k] while the cheaper Ru(II) complexes are by far much less studied.[12g,j,13]

The use of unprotected primary amines as directing groups, for example, the $-CH(R_4)NH_2$ moiety shown in eq 3 of Scheme 1 has not been reported before. We found that (hetero)aryl-containing primary amines are suitable precursors for the synthesis of our target isoquinolines, thienopyridines and other fused heteroarylpyridines, since they are very accessible and well-known, most of them are commercially available or can be prepared through well established synthetic procedures with a wide scope of different substituents and, in general, they are stable against the oxygen and the moisture (in contrast, for instance, with imines or oximes) and available in bulk quantities. Moreover, primary amines are actually susceptible to be orthometalated by transition metals,[14] and we have selected the inexpensive ruthenium catalysts because there are precedents of such metalation.[14a] We disclose here our results on the synthesis of a wide variety of isoquinolines, benzoquinolines and fused bis-heterocycles by an unprecedented reaction of amine-based (hetero)aryl derivatives with internal alkynes catalyzed by Ru(II) derivatives.

RESULTS AND DISCUSSION

Catalytic Synthesis of Fused Heteroarylpyridines. The coupling of thiophene-2-methylamine **1a** with 3-hexyne **2a**, catalyzed by $[Ru(p\text{-cymene})Cl_2]_2$ (**Ru**), was used as model reaction for process optimization. The obtained results are shown in Table 1. We have started using the conditions previously reported by us for the C−H activation of thiophene-imines (toluene, 80 °C, 24 h),[15] but using a 10% (in mol) of **Ru** with respect to **1a** and $Cu(OAc)_2$ as oxidant in excess (entry 1). Under these conditions, the 2-cyano-3-vinylthiophene **5aa** was obtained, showing that the amine oxidation, probably also catalyzed by Ru,[16a] occurs faster than the C−H activation, insertion, and annulation steps. We then change the solvent to methanol, which gave good results in the annulation of alkynes with orthoruthenated thiophene-imines using stoichiometric

Table 1. Optimization of the Reaction Conditions for the Synthesis of 3aa[a]



entry	solvent	additive[b]	T (°C)/time (h)	3aa/4aa/5aa[c]
1	toluene	$Cu(OAc)_2$[d]	80/24	−/−/65
2	methanol	$Cu(OAc)_2$[d]	80/24	75/25/−
3	dichloroethane	$Cu(OAc)_2$[d]	80/24	−/−/15
4	methanol	$PhI(OAc)_2$	80/24	−/−/10
5	methanol	$Cu(OAc)_2$	80/24	97/−/−
6	methanol	$Cu(OAc)_2$[e]	80/24	98/−/−
7	methanol	$Cu(OAc)_2$[f]	80/24	71/−/−
8	methanol	$Cu(OAc)_2$	80/6	64/−/−
9	methanol	$Cu(OAc)_2$	100/6	97/−/−

[a]Standard reaction conditions: **1a** (1 mmol), **2a** (2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (**Ru**; 0.1 mmol), KPF_6 (0.1 mmol), and the additive (1 mmol) were dissolved in the solvent and heated at the indicated temperature during the specified time. [b]Equimolar with respect to **1a**. [c]Isolated yields (%). [d]2 mmol. [e]3 mmol of **2a**. [f]1 mmol of **2a**.

Ru.[15] Gratifyingly, a mixture of 4,5-diethylthieno[2,3-*c*]pyridine **3aa** (75% yield) and the corresponding 7-methoxylated derivative **4aa** (25% yield) was obtained (entry 2), the two compounds being easily separated by column chromatography. Further screening of different solvents did not afford **3aa** or **4aa** (entry 3) since only **5aa** was detected in variable amounts. Therefore, MeOH was shown to be the optimal solvent, although the formation of **4aa** through nucleophilic attack of a methoxide anion to the iminic carbon of **3aa** and rearomatization has to be minimized or suppressed.

Among the different oxidants tested for this process, $Cu(OAc)_2$ was shown to be the best choice, since other strong oxidants such as $PhI(OAc)_2$ promotes the fast oxidation of the amine to the nitrile group (entry 4) and **5aa** was formed together with other unidentified products.[16b] Moreover, $Cu(OAc)_2$ plays also the role of source of acetate ligands, needed for an efficient C−H activation of **1a**.[17] Other sources of acetate ligands, such as NaOAc, or other copper salts did not afford successful results. The amount of $Cu(OAc)_2$ has also a critical effect on the outcome of the reaction. We have found that the use of an equimolar ratio **1a**/Cu produces **3aa** as the unique reaction product (entry 5) in very good yields. Under these reaction conditions the methoxylated **4aa** was not observed. The amount of alkyne has also been optimized, and a 2:1 molar ratio (**2a**:**1a**) appears to be the best ratio. An increase in the amount of alkyne (3:1 molar ratio) does not produce a noticeable improvement of the yield of **3aa** (entry 6), while a decrease of **2a** (1:1 molar ratio) drops the yield of **3aa** (entry 7). Further optimization has been focused on the correct choice of the temperature and time of the reaction. The decrease of the reaction time from 24 h to 6 h produces only a moderate yield of **3aa** (entry 8), which was clearly improved up to 97% (entry 9) increasing the reaction temperature to 100 °C. With the optimized conditions in hand, we tested the reaction scope, using a variety of heterocycles **1** and internal alkynes **2**. The results obtained using 3-hexyne **2a** but changing the heterocycle **1** are shown in Scheme 2.

The reaction tolerates the presence of substituents at 5-position of the thiophene ring, both electron-donating (**3ba**) and electron-withdrawing (**3da**), although better yields were

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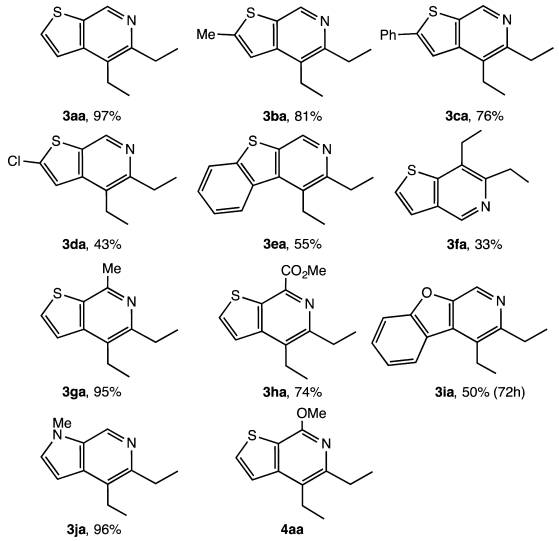
Scheme 2. Scope of Heterocycle-Fused Pyridines 3 Changing the Heterocycle 1

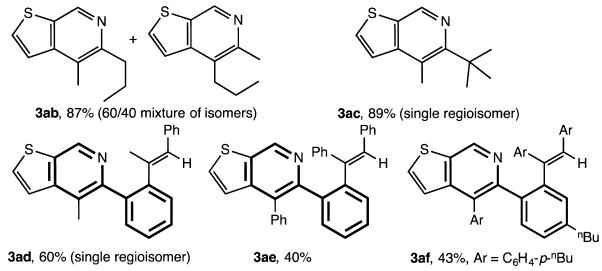


obtained for the formers, as expected according to previous work of Pfeffer et al.[18] In the same way, benzothiophene-methylamine reacts to give the fused tris-heterocycle **3ea** in a 55% yield. This lower reactivity of the benzannulated derivative also agrees with previous results.[15] From the precursor thiophene-3-methylamine **1f** only the isomer 6,7-diethylthieno-[3,2-*c*]pyridine **3fa** was obtained, in keeping with the easier ruthenation at the more active 2-position of the thiophene ring, compared with the 4-position. The reaction also tolerates substituents at the α-position of the 2-methylamino directing group, regardless their electronic nature, and good yields were obtained when methyl (**3ga**) or carbomethoxy (**3ha**) moieties are present. It is also quite remarkable that the scope of the reaction could be expanded to other electron-rich heterocycles.

Fused bis-heterocycle **3ja** derived from pyrrole was isolated in 96% yield, while the tricyclic **3ia**, prepared from benzofuran, was obtained in 50% yield. It is necessary to remark that benzofurane derivatives need longer reaction times to achieve similar yields due to its lower reactivity. Surprisingly, in the case of the indole-amine derivative we constated a total lack of reactivity. We are not aware about the reasons of this behavior, because we have shown that orthoruthenated indole-imines react with alkynes to give pyrido[3,4-*b*]indolium salts.[15]

Concerning the scope of alkynes **2**, alkylic electron-rich species such as 3-hexyne (**2a**), 2-hexyne (**2b**) and 4,4-dimethyl-2-pentyne (**2c**) reacts straightforwardly with **1a** to give the corresponding 4,5-dialkylthieno[2,3-*c*]pyridines **3aa**−**ac** shown in Scheme 3 in moderate to excellent yields. Another classical electron-rich alkyne, as is $Me_3SiC{\equiv}CSiMe_3$, was also tested. However, due to the fact that the reaction is performed in refluxing methanol, full decomposition of the alkyne by methanolysis was observed. When nonsymmetrical alkynes are used, the selectivity of the insertion depends largely on steric factors.[19] Thus, the reaction of **1a** with 2-hexyne (**2b**) results in a 60:40 mixture of the two isomers of **3ab**, due to the similarity between the methyl and *n*-propyl fragments, while in the case of the reaction of **1a** with 4,4-dimethyl-2-pentyne (**2c**) **3ac** is obtained regioselectively in 89% yield. The stereochemistry of **3ac** has been determined by the observation of a NOE effect (Supporting Information) between the signals at 2.69 ppm (4-Me) and 7.34 ppm (H3).

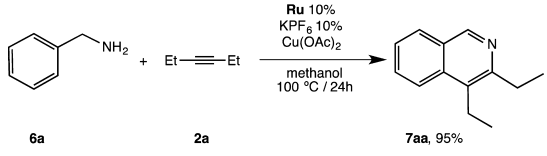
Scheme 3. Scope of Heterocycle-Fused Pyridines 3 Changing the Alkyne 2



In clear contrast with the selective insertion of one alkyne observed in **3aa**−**ja** and **3ab**−**ac**, the reaction of **1a** with aryl-containing alkynes, for instance PhC≡CMe (**2d**) or PhC≡CPh (**2e**), goes one step beyond. The first insertion produces a 5-phenylthieno[2,3-*c*]pyridine core, with an additional alkyl/aryl substituent at the 4-position. It is very remarkable that this first insertion occurs with full regioselectivity in the case of alkyne **2d**, showing that steric hindrance is not the only operative factor in the control of the regioselectivity. This core is formally analogous to a 2-phenylpyridine ligand, which is amenable to undergo a further C−H activation regioselectively at the *ortho* position of the 5-phenyl ring and a second alkyne insertion to give the corresponding alkenylated derivative.[20] This scarce double insertion is quite remarkable and provides a new pathway to the more complex structures **3ad**−**af** shown in Scheme 3. In all studied cases the basic structure thus obtained is a 5-arylthieno[2,3-*c*]pyridine *ortho*-alkenylated at the 5-aryl ring. It is worthy of note that the synthesis of 5-arylthieno[2,3-*c*]pyridines is known,[12] but that here reported for the *ortho*-olefinated derivatives is unprecedented. Symmetrical alkynes obviously affords single compounds, as is the case of PhC≡CPh (**2e**) and *p*-^{n}BuC$_6$H$_4$C≡CC$_6$H$_4$-*p*-^{n}Bu (**2f**), which give **3ae** and **3af**, respectively. Obviously, this additional reactivity further expands the synthetic applicability of this method.

Catalytic synthesis of isoquinolines. Prompted by the excellent results obtained in the synthesis of fused heteroaryl pyridines, we have explored additional possibilities, aiming to give more generality to the method. Therefore, other primary amines have been subjected to Ru-catalyzed dehydrogenative coupling with different internal alkynes. Benzylamines have shown to be very good starting materials for this type of coupling. The reaction of benzylamine **6a** with 3-hexyne **2a**, under the conditions described in Table 1, affords isoquinoline **7aa** in low yield, with most of the starting amine **6a** being recovered unchanged. The solvent, temperature, and reaction time were varied in order to optimize this process. We found that this low conversion can be improved notably if the reaction time is prolongued up to 24 h at the same temperature (100 °C). Under these conditions, **7aa** is obtained analytically pure in 95% yield, as represented in Scheme 4. Other changes produced lower yields of the target product **7aa**, contaminated

Scheme 4. Synthesis of 3,4-Diethylisoquinoline 7aa and Optimized Reaction Conditions



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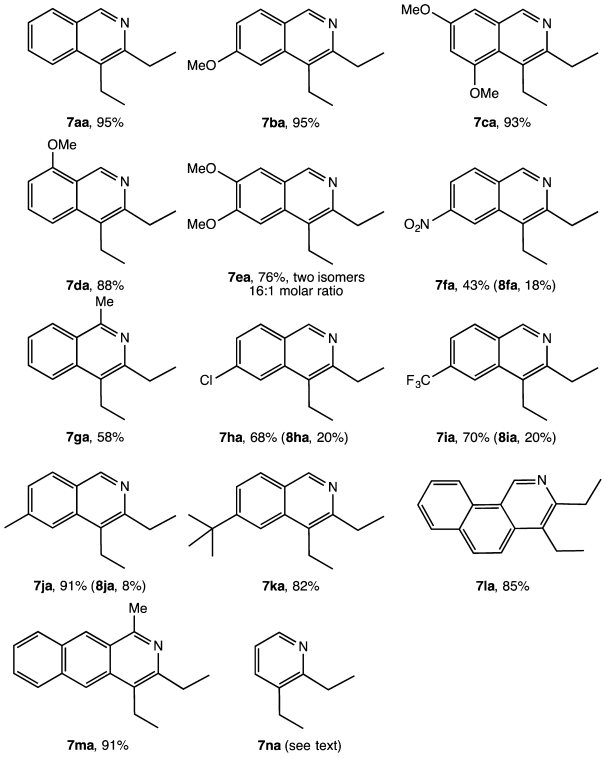
with variable amounts of byproducts or with starting amine **6a**. Therefore, the experimental conditions shown in scheme 4 were used as the optimized conditions. The larger reaction times involved here, compared with those required for the heterocycles **1** (24 h vs 6 h) suggest that the reaction is favored for electron-rich substrates.

A wide variety of substituted benzylamines **6** have been reacted with 3-hexyne **2a** in order to check the scope of the reaction, changing the nature and the position of the substituents. The results are shown in Scheme 5. In the case

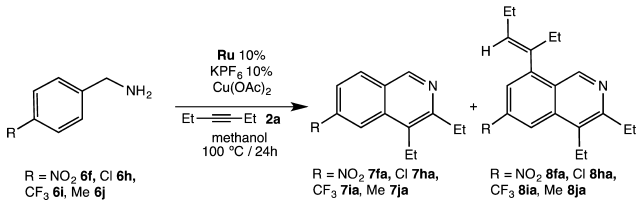
Scheme 5. Scope of Isoquinolines 7 Changing the Benzylamine 6



of electron-releasing groups, very good yields were obtained in all attempted cases, better (in general) than those described in the previous section for the fused heteroarylpyridines. For instance, the presence of one methoxy group either in *para* (**7ba**) or in *ortho* (**7da**) to the cyclometalation position gives the corresponding isoquinolines in similar high yields (95% vs 88%). The presence of two methoxy groups in the two meta 3,5-positions does not hinder the C−H activation and allows for the synthesis of **7ca** in a remarkable 93% yield. When the two methoxy groups are in positions 3 and 4 two cyclometalation sites are available. Compound **7ea** is thus obtained in 76% yield as the mixture of the two possible isomers, although one of them is clearly favored (16:1 molar ratio, Scheme 5). This high selectivity is easily explained taking into account that the less sterically hindered C−H bond in the cycloruthenation step (in this case the 6-position) is preferentially activated.[21] Other electron-donating alkyl groups (Me, *t*Bu) give also the corresponding 3,4,6-trisubstituted isoquinolines in good to excellent yields, regardless the alkyl substituent is on the aryl ring (**7ja** and **7ka**, 91% and 82% yield, respectively) or at the Cα position (**7ga**, 58%).

It is noteworthy that during the synthesis of compound **7ja** we have detected a minor second component in the crude of the reaction (**8ja**, 8%), which can be separated from the main product **7ja** by column chromatography. The analytic and spectroscopic data of **8ja** show that a second alkyne molecule has been incorporated at the benzo ring of the isoquinoline **7ja**, introducing a vinyl substituent at the 8-position. This process, shown in Scheme 6, can be formally considered as the hydroarylation of 3-hexyne, being the aryl unit the isoquinoline **7ja**.

Scheme 6. Reactivity of Benzylamines To Give Isoquinolines 7 and 8-Vinylisoquinolines 8



The same result is observed when the starting benzylamine **6** has strong electron-attracting substituents, such as nitro (**6f**), chloro (**6h**) of CF_3 (**6i**). In all three cases, a mixture of the isoquinolines **7** and the corresponding 8-vinylisoquinolines **8** was obtained (Scheme 6), being always **7** the main component of the mixture (Scheme 5). Compounds **7** can be obtained in analytically pure form by column chromatography (see Supporting Information), while minor components **8** were always mixed with small (but detectable) amounts of **7**, precluding the characterization of **8** in pure form. On the other hand, the molar ratio **7**/**8** changes as a function of the substituent. While in the case of the methyl group we isolate only an 8% of **8ja**, the yield of **8fa**, **8ha** and **8ia** after chromatographic separation is around 20%. The selectivity observed in the incorporation of the second alkyne moiety at the 8-position is remarkable, and no other isomers were detected. It is also relevant the fact that when methoxy substituents are present in the benzylamine (**6b−e**) no vinylation products were detected, neither in the case of the unsubstituted **6a**, even at the level of traces.

Other substrates were also investigated. 1-Naphthylmethylamine **6l** reacts with 3-hexyne affording the benzo[*h*]isoquinoline **7la** (Scheme 5), while the related 1-(2-naphthyl)ethylamine **6m** gives the corresponding benzo[*g*]isoquinoline **7ma** with excellent yields in both cases (85% and 91%, respectively). The reaction occurs in both cases with full regioselectivity. In the case of amine **6l** the reason of this selectivity could reside in the competitive activation of the C−H bonds at the 2- and 8-positions and further alkyne insertion and annulation. This reactivity at 2-position affords the aromatic 6-membered benzo[*h*]isoquinoline **7la**, while that at 8-position would give a nonaromatic, and then probably less favored, 7-membered naphthoazepine. In addition, allylamine **6n** reacts, under the standard reaction conditions, to give the 2,3-diethylpyridine **7na**. Despite the full conversion observed, and only in this case, the purification of **7na** proved to be very difficult and the pure compound could not be isolated.

The scope of available isoquinolines **7** changing the alkyne **2** follows similar trends than those described previously for the fused pyridines. Therefore, alkylic electron-rich species such as 3-hexyne (**2a**), 2-hexyne (**2b**), and 4,4-dimethyl-2-pentyne (**2c**)

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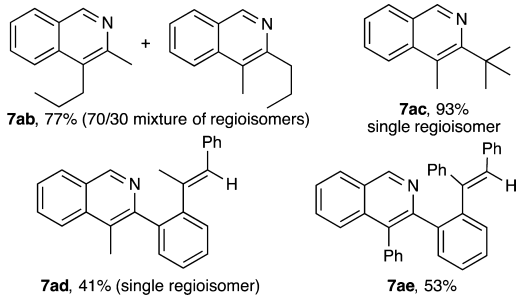
afford the corresponding isoquinolines **7aa–ac** (Scheme 7) in moderate to excellent yields. Compound **7ab** is obtained as the

Scheme 7. Scope of Isoquinolines 7 Changing the Alkyne 2

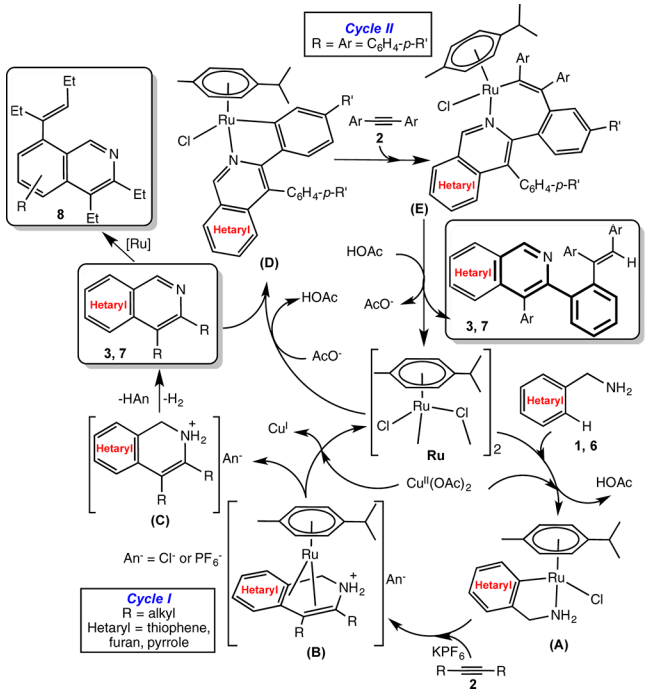


mixture of regioisomers (70/30), improving the selectivity observed in **3ab** (60/40), while **7ac** is obtained regioselectively as the 3-*t*-Bu-4-Me isomer.

In the same way as described in preceding paragraphs for fused pyridines **3ad–af**, the reaction of benzylamine **6a** with aryl-containing alkynes such as PhC≡CMe (**2d**) or PhC≡CPh (**2e**) occurs with insertion of two alkynes. The first insertion affords the expected 3,4-diphenylisoquinoline, which further undergoes a second C–H bond activation at the 3-phenyl ring and the subsequent insertion of the alkyne to give the olefinated derivatives **7ad** and **7ae**.[20] Remarkably, the insertion of PhC≡CMe (**2d**) is once again regioselective, and **7ad** is the only observed isomer.

Mechanistic Considerations. In the preceding paragraphs, we have described the reactivity of primary amines such as benzylamines and aminomethyl-heterocycles toward internal alkynes, allowing for the obtention of, at least, four different types of products: (i) fused heteroaryl-pyridines (**3aa–ja**, **3ab–ac**); (ii) isoquinolines (**7aa–ma**, **7ab–ac**); (iii) thienopyridines and isoquinolines *ortho*-vinylated at the 3-phenyl ring (**3ad–af**, **7ad–ae**); and (iv) isoquinolines vinylated at the 8-position (**8fa–ja**). The synthesis of the fused heteroarylpyridines (**3**) and isoquinolines (**7**) from the unprotected primary amines (**1** or **6**, respectively) and alkynes **2** implies not only the C–H activation at the aromatic ring but also the dehydrogenation and deprotonation of the CH_2NH_2 moiety with concomitant obtention of an aromatic molecule. Aiming to gain more insight into the mechanism of the catalytic cycle, we have monitored the reaction of **1a** with **2a** by ^{1}H NMR spectroscopy in CD_3OD at 60 °C. The disappearance of one of the signals assigned to the thiophene ring in **1a** and the observance of an AB spin system for the diastereotopic CH_2N protons strongly suggest that orthoruthenation of amine **1a** has taken place and that the resulting cyclometalated ligand is located on an asymmetric environment, such as that depicted in Scheme 8 (cycle I) for species (**A**) (see the Supporting Information). This proposal is based on previous work of Pfeffer et al.[18] and on our own work.[15] The detection of species (**A**) also suggests that this is the resting state of the catalyst, and that the limiting rate step is the insertion of the alkyne in the Ru–C bond, in good agreement with previous results.[18b] More importantly, these observations strongly suggest that the dehydrogenation of the CH_2NH_2 directing group is produced *after* the C–H bond activation step, probably at the latest stages of the reaction and without the participation of the metal.[22] If the dehydrogenation of **1a** occurred *prior* to the C–H bond activation, it would produced a thiophene-imine. We have shown recently that the

Scheme 8. Mechanistic Proposal for the Synthesis of Compounds 3, 7, and 8



orthoruthenation of thiophene-imines is possible, but also that it takes some hours, therefore the presence of free imine should be evident in the first steps of the reaction. However, the ^{1}H NMR spectrum of the reaction mixture (see the Supporting Information) does not show signals in the 8–9 ppm region, where the N=CH iminic protons usually appears. On the other hand, the orthoruthenation of imines affords very stable complexes, even characterized by X-ray methods.[15] However, all attempts to isolate an analogous metalated complex from **1a** under the catalytic conditions were not successful. Moreover, we have performed additional control experiments in order to determine which could be the conditions for hypothetical imine formation. The treatment of free amine **1a** in CD_3OD at 100 °C for 6h does not promote any evident change on the ^{1}H NMR spectrum, giving proof of the stability of this material under the reaction conditions. When **1a** is heated in the presence of $Cu(OAc)_2$, the formation of imine was not detected either, and the same result is obtained after heating of **1a** with the dimeric species $[Ru(cym)Cl_2]_2$. In the latter, the change of the shape and the position of the peaks due to the three protons of the thiophene moiety was observed, suggesting the interaction of this fragment with the Ru species (probably through N-coordination). All these facts militate against the participation of imines in the catalytic cycle, and in favor of the amine involvement.

We can tentatively close the catalytic cycle I by similarity with previous works. Therefore, we suggest that (**A**) reacts with KPF_6 generating a vacant coordination site. Alkyne **2** bonds in this vacant site, and further undergoes a migratory insertion process followed by C–N reductive coupling giving Ru(0) species (**B**). The exact nature of intermediate (**B**) is not known, but it is proposed to be a η^4-dehydroisoquinolinium Ru(0) intermediate by analogy with previous work of Pfeffer.[18] Other recent proposals for the alkyne insertion on cycloruthenated imines are based on Ru(II) species,[15] but they do not apply here due to the different nature of the amine vs imine as

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directing groups. Smooth oxidation of (**B**) with Cu(II) releases the dihydropyridinium cation (**C**) and regenerates the catalyst **Ru**.[23] The elimination of HCl from (**C**) and subsequent dehydrogenation of the dihydropyridine intermediate to give the bicyclic structures **3** or **7** likely occurs under the reaction conditions without participation of the metallic catalyst.

A second alkyne incorporation occurs in compounds derived from the insertion of diarylacetylenes, affording species **3ad**−**af**, **7ad** and **7ae**. The mechanistic proposal for these processes is shown in Scheme 8, cycle II. Therefore, once the first insertion has taken place, a new Ru-mediated C−H bond activation can occur at the *ortho* C−H bond of the aryl ring located on the carbon adjacent to the N atom, affording presumably the intermediate (**D**). Obviously, the pyridinic nitrogen behaves as a directing group. Compound (**D**) can then react with an additional equivalent of internal alkyne giving (**E**), which is protonated at the vinyl carbon releasing the formally hydroarylated derivatives **3** or **7**, as a function of the starting amine. It is quite remarkable that, as far as we know, the hydroarylation of internal alkynes using 2-phenylpyridine as aryl source has been catalyzed with Rh(I) or Co(II), but never with Ru(II) complexes.[24]

While the *ortho*-vinylation of the 3-Ph ring has been observed in fused heteroaryl-pyridines **3** and isoquinolines **7**, some isoquinolines **7** have shown an additional reactivity pattern for the incorporation of a second alkyne (**7fa**,**ha**−**ja**), which takes place specifically at 8-position of the benzo ring. Both facts, the substitution at the benzo ring and its occurrence at the 8-position, strongly suggest that this 8-vinylation is a Ru-mediated process where the ruthenation step occurs through an aromatic electrophilic substitution mechanism (S_EAr). Once the Ru moiety has been incorporated to the benzo ring, the coordination of the alkyne, followed by its migratory insertion and protonation of the vinyl intermediate, as described for the previous case, will result in the formation of species **8**, similarly to what is shown in Scheme 8 as cycle II. An alternative mechanism to explain the formation of species **8** should involve the protonation of the metalated vinyl-intermediate previous to the N−C coupling in **B**, this reaction affording an *ortho*-alkenylbenzylamine. Further C−H activation of the H6 proton followed by a second alkyne insertion through cycle I would afford the 8-vinyl-substituted isoquinolines **8**. However, this second mechanism does not seem to be operative on the following grounds. First, we have stopped the reaction at short reaction times, when it is more likely to find the *o*-alkenylbenzylamine, but we have not spectroscopic evidence for the formation of this product; however, isoquinolines **7** were already present in the reaction mixture from the very beginning of the reaction. Second, the first alkyne insertion should give two competitive products, the isoquinolines **7** and the *o*-alkenylbenzylamines; however, there are cases where conversion of benzylamine is complete and **7** can be isolated in 95% yield, rendering the process weakly favorable for the formation of the *o*-alkenylbenzylamine. Third, if after the first insertion the favored process is the protonation and formation of the *o*-alkenylbenzylamine, then after the second insertion the same process should occur, because the directing group is exactly the same. Therefore the bis-*o*-alkenylbenzylamine should be expected as reaction product, and the isoquinolines should not be observed; obviously, this is not the case and our proposal is that shown in Scheme 8.

In addition, the observed distribution of products **7**/**8** and the selectivity of the vinylation at 8-position in **8** merits a more detailed analysis. In principle, when an electron-releasing group, such as methyl, *tert*-butyl or methoxy, is present at 6-position of **7**, the electrophilic substitution at 5-position should be favored on electronic grounds with respect to that at 8-position, while the steric hindrance exerted by the 4- and 6-substituents hampers the reaction at 5-position and should direct the reactivity to the less favored 8-position. Therefore the final activated site should be the result of a delicate balance between the two factors. In the light of the observed reactivity, it seems that in the presence of electro-donating groups the steric factors prevail over the electronic ones. Therefore, when bulky substituents such as *tert*-butyl, or even not so bulky but strongly donating such as methoxy, are present, the substitution at 5-position is blocked sterically while that at 8 is not favored electronically, and then the 8-vinyl derivatives **8** are not formed at all, or only in a very low amount (**8ja**, 8%). It is clear that **7aa** escapes to this argument, but we are unaware about the reasons of the lack of reactivity for this species. However, when the substituent located at 6-position has an electron-withdrawing character, the electrophilic substitution at 8-position (vs 5-position) is favored both on electronic and steric grounds, and therefore, the 8-vinyl derivatives **8** are obtained in a 20% yield. The low yield for species **8** also suggests that the rate of the vinylation of compounds **7** is much slower than that of the annulation of benzylamines **6** to give **7**, and therefore, isoquinolines **7** are the main product of the reaction.

■ CONCLUSION

Primary amines, such as benzylamines, naphthylmethylamines, naphthylethylamines, heteroarylmethylamines, or even allyl amines, substituted at various positions, are good starting materials for the synthesis of a wide variety of isoquinolines, benzoisoquinolines, and fused heteroarylpyridines. In addition of the broad range of targeted compounds achievable, different isomers of each one are accessible, and the presence of a large number of electron-attracting and -releasing substituents in different positions is tolerated. The method is based on the directed C−H bond activation of a broad range of unprotected primary amines as efficient directing groups, followed by dehydrogenative coupling with internal alkynes, all processes catalyzed by Ru(II) complexes. The method is actually competitive with standard organic procedures, and further development and expansion to other interesting substrates, such as alkenes, is currently being under study.

■ EXPERIMENTAL SECTION

General Methods. Solvents were used as received from commercial sources. They were not distilled nor subjected to additional purification. All reactions were carried out without protecting atmosphere. Column liquid chromatography were performed on aluminum oxide 90 neutral (50−200 μm) or silica gel (70−230 μm). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 25 °C on spectrometers (δ in ppm, J in Hz) at ^{1}H operating frequency of 400.13 MHz. ^{1}H and ^{13}C spectra were referenced using the solvent signal as internal standard. The assignment of ^{1}H NMR peaks has been performed through standard 2D ^{1}H−COSY (2K points in t_2 using a spectral width of 10 ppm; 128 t_1 experiments were recorded and zero-filled to 1K; for each t_1 value four scans were signal-averaged using a recycle delay of 1 s) and selective 1D ^{1}H-NOESY experiments. Typical mixing times in the case of selective 1D-NOESY experiments were 800 ms or 1s, as a function of the irradiated signal. These values of optimized mixing times were set equal to the longitudinal relaxation time T_1, which in turn was determined using the inversion−recovery sequence. Once the ^{1}H

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NMR signals were fully assigned, the corresponding ^{13}C NMR peaks were identified using standard $^{1}H-^{13}C$ edited-HSQC and $^{1}H-^{13}C$ HMBC 2D-experiments. In both cases 4*K* points in t_2 using spectral widths of 10 ppm (^{1}H) and 220 ppm (^{13}C) were used, with averaged values of the coupling constants $^{1}J_{CH}$ = 145 Hz and long-range $^{n}J_{CH}$ = 8 Hz. Typically 512 t_1 experiments were recorded and zero-filled to 2*K*. For each t_1 value 16 scans were signal-averaged using a recycle delay of 2 s. HRMS and ESI (ESI+) mass spectra were recorded using an MicroToF Q, API-Q-ToF ESI with a mass range from 20 to 3000 *m*/*z* and mass resolution 15000 (fwhm). The synthesis of the ruthenium catalyst $[Ru(p\text{-cymene})(\mu\text{-Cl})Cl]_2$[25] and amines **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1i**, and **1j**[26] have been carried out following published procedures. Other starting amines **1** and **6** and alkynes were purchased from commercial sources.

Typical Experimental Procedure for the Fused Heterocycle–Pyridines 3. The corresponding heterocycle-methylamine **1** (1 mmol) and alkyne **2** (2 mmol) were added to a solution of $[Ru(p\text{-cymene})Cl_2]_2$ (0.061 g, 0.1 mmol), $[Cu(OAc)_2]$ (0.181 g, 1.0 mmol), and $K[PF_6]$ (18.7 mg, 0.1 mmol) in MeOH (3 mL) into a Young's flask. The solution was then heated at 100 °C for 6h. After that, the solvent was removed and the residue subjected to flash chromatography on neutral alumina eluting with DCM (DCM = CH_2Cl_2), then DCM/MeOH (95:5). Both eluted fractions were mixed and evaporated to dryness, affording **3** as oily materials or waxy solids, which were washed with Et_2O (10 mL) and pentane (10 mL). Compounds **3da**, **3ab** and **3ae** were further purified by a second column chromatography on silica gel eluting with mixtures hexane/ethyl acetate (9/1 to 1/1).

3aa. Yellow oil (186 mg, 97% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.21 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.27 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.87 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.91 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 7.31 (1H, dd, $^{3}J_{HH}$ 5.2 Hz, $^{4}J_{HH}$ 0.8 Hz, H_{thio}), 7.58 (1H, d, $^{3}J_{HH}$ 5.2 Hz, H_{thio}), 8.88 (1H, s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.8, 15.1, 22.9, 27.5, 121.4, 130.2, 131.3, 134.2, 141.7, 145.0, 153.9. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 192. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{14}NS$ 192.0847, found 192.0842.

3ba. Yellow oil (167 mg, 81% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.18 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.25 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.55 (3H, d, $^{4}J_{HH}$ 1.2 Hz, CH_3), 2.82 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.83 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 6.96 (1H, $^{4}J_{HH}$ quintuplet, 1.2 Hz, H_{thio}), 8.70 (1H, s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.7, 15.0, 16.5, 22.8, 27.5, 119.3, 129.3, 134.3, 140.8, 145.9, 146.5. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 206. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{16}NS$ 206.1003, found 206.1005.

3ca. Yellow wax (203 mg, 76% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.24 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.28 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.87 (4H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.93 (4H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 7.3 (1H, m, ArH), 7.4 (2H, m, ArH), 7.50 (1H, d, 0.8 Hz, H_{thio}), 7.7 (2H, m, ArH), 8.82 (1H, s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 13.7, 14.1, 21.8, 26.6, 115.8, 125.9, 128.0, 128.1, 128.9, 132.7, 132.8, 140.3, 144.9, 148.4, 153.3. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 268. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{18}NS$ 268.1160, found 268.1151.

3da. Yellow oil (97 mg, 43% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.23 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.31 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.87 (4H, q, $^{3}J_{HH}$ 7.8 Hz, CH_2CH_3), 2.89 (4H, t, $^{3}J_{HH}$ 7.8 Hz, CH_2CH_3), 7.22 (1H, s, H_{thio}), 8.73 (1H, s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.5, 15.0, 22.8, 27.6, 120.6, 129.5, 133.3, 137.6, 140.4, 144.0, 154.9. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 226. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{13}ClNS$ 226.0457, found 226.0439.

3ea. Yellow wax (134 mg, 55% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.27 (3H, t, 7.6 Hz, CH_2CH_3), 1.31 (3H, t, 7.6 Hz, CH_2CH_3), 2.87 (2H, q, 7.6 Hz, CH_2CH_3), 2.92 (2H, q, 7.6 Hz, CH_2CH_3), 7.4 (2H, m, ArH), 7.8 (1H, m, ArH), 8.1 (1H, m, ArH), 9.12 (1H, s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 12.4, 13.4, 24.0, 26.7, 120.5, 121.8, 124.0, 126.1, 129.1, 129.1, 133.7, 137.9, 139.6, 147.6, 155.8. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 242. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{15}NS$ 242.1003, found 242.0998.

3fa. Yellow oil (66 mg, 33% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.26 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.28 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.87 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.88 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 7.33 (2H, m, H_{thio}), 8.85 (1H, s). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 13.6, 14.6, 24.8, 27.5, 123.1, 126.4, 129.7, 134.5, 136.8, 142.8, 153.5. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 192. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{14}NS$ 192.0847, found 192.0841.

3ga. Yellow wax (195 mg, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.16 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.23 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.65 (3H, s, CH_3), 2.83 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.85 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 7.28 (1H, d, $^{3}J_{HH}$ 5.6 Hz, H_{thio}), 7.49 (1H, d, $^{3}J_{HH}$ 5.6 Hz, H_{thio}). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.2, 14.3, 21.7, 22.3, 26.6, 121.1, 126.7, 129.4, 132.2, 143.9, 148.3, 152.9. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 206. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{16}NS$ 206.1003, found 206.0998.

3ha. Orange oil (185 mg, 74% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.22 (3H, t, 7.6 Hz, CH_2CH_3), 1.28 (3H, t, 7.6 Hz, CH_2CH_3), 2.97 (2H, q, 7.6 Hz, CH_2CH_3), 2.98 (2H, q, 7.6 Hz, CH_2CH_3), 4.01 (3H, s, $COOCH_3$), 7.36 (1H, d, 5.6 Hz, H_{thio}), 7.68 (1H, d, 5.6 Hz, H_{thio}). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.9, 15.1, 23.3, 27.7, 53.1, 120.8, 134.6, 134.8, 135.2, 139.0, 146.8, 154.9, 166.3. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 250. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{16}NSO_2$ 250.0902, found 250.0920.

3ia. Yellow wax (113 mg, 50% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.27 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.28 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.90 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 3.06 (3H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 7.29 (1H, td, $^{3}J_{HH}$ 7.6 Hz, $^{4}J_{HH}$ 1.2 Hz, ArH), 7.46 (1H, td, $^{3}J_{HH}$ 7.6 Hz, $^{4}J_{HH}$ 1.2 Hz, ArH), 7.5 (1H, d, $^{3}J_{HH}$ 7.6 Hz, ArH), 7.93 (1H, d, $^{3}J_{HH}$ 7.6 Hz, ArH), 8.66 (1H, s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 13.9, 14.8, 22.6, 27.3, 112.4, 122.6, 123.2, 123.4, 128.9, 129.6, 130.8, 131.1, 151.4, 154.1, 156.9. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 226. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{16}NO$ 226.1232, found 226.1226.

3ja. Yellow wax (181 mg, 96% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.18 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.23 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.82 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.84 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 3.74 (3H, s, NCH_3), 6.36 (1H, d, $^{4}J_{HH}$ 2.8 Hz, H_{pyrr}), 7.05 (1H, d, $^{4}J_{HH}$ 2.8 Hz, H_{pyrr}), 8.47 (1H, s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 15.0, 15.2, 22.5, 27.2, 33.1, 98.9, 127.3, 129.5, 132.3, 132.5, 134.0, 148.4. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 189. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{17}N_2$ 189.1392, found 189.1386.

4aa. Yellow oil (55 mg, 25% as byproduct of **3aa**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.15 (3H, t, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 1.25 (3H, t,, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.75 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 2.81 (2H, q, $^{3}J_{HH}$ 7.6 Hz, CH_2CH_3), 4.02 (3H, s, OCH_3), 7.27 (1H, d, $^{3}J_{HH}$ 5.2 Hz, H_{thio}), 7.51 (1H, d, $^{3}J_{HH}$ 5.6 Hz, H_{thio}). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.4, 15.4, 22.4, 26.9, 53.2, 120.2, 122.0, 130.4, 147.8, 151.4, 156.1. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 222. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{16}NOS$ 222.0953, found 222.0945.

3ab (Both Isomers). yellow oil (167 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 0.92 (t, $^{3}J_{HH}$ 7.6 Hz, $CH_2CH_2CH_3$, both), 1.50 (m, $CH_2CH_2CH_3$), 1.71 (m, $CH_2CH_2CH_3$), 2.44 (s, CH_3), 2.55 (s, CH_3), 2.80 (m, $CH_2CH_2CH_3$), 2.81 (m, $CH_2CH_2CH_3$), 7.25 (d, $^{3}J_{HH}$ 5.6 Hz, H_{thio}, both), 7.50 (d, $^{3}J_{HH}$ 5.6 Hz, H_{thio}, both), 8.80 (s, CHN), 8.83 (s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.2, 14.3 15.2, 21.4, 23.0, 23.2, 32.1, 37.0, 121.4, 121.6, 124.2, 129.4, 131.1, 131.2, 133.8, 134.2, 141.2 (2C), 145.6 (2C), 149.1, 153.2. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 192. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{14}NS$ 192.0847, found 192.0842.

3ac. Yellow wax (183 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.45 (9H, s, $C(CH_3)_3$), 2.69 (3H, s, CH_3), 7.34 (1H, dd, $^{3}J_{HH}$ 5.2 Hz, $^{5}J_{HH}$ 0.4 Hz, H_{thio}), 7.55 (1H, d, $^{3}J_{HH}$ 5.6 Hz, H_{thio}), 8.85 (1H, s, CHN). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 17.8, 30.7, 38.4, 27.5, 121.9, 124.8, 130.7, 133.8, 139.8, 147.1, 158.8. $(ESI)^+$ *m*/*z*: $[M + H]^+$ (100) 206. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{16}NS$ 206.1003, found 206.0998.

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3ad. Yellow oil (205 mg, 60% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.83 (3H, s, CH_3), 2.42 (3H, s, CH_3), 6.4 (1H, m, H_{alkene}), 7.1 (2H, m, ArH), 7.2 (1H, m, ArH), 7.3 (2H, m, ArH), 7.4−7.5 (5H, m, ArH), 7.73 (1H, d, $^3J_{HH}$ 5.4 Hz, H_{thio}), 9.09 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 16.4, 19.2, 122.0, 125.4, 126.2, 126.9, 127.9, 128.0, 128.3, 128.7, 130.3, 130.4, 131.6, 134.8, 138.1, 138.6, 138.8, 141.2, 145.3, 145.4, 152.7. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 342. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{20}NS$ 342.1316, found 342.1323.

3ae. Yellow wax (186 mg, 40% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.89 (1H, s, H_{alkene}), 6.4 (2H, m, ArH), 6.78 (4H, m, ArH), 6.90 (1H, tt, $^3J_{HH}$ 7.6 Hz $^4J_{HH}$ 2.4 Hz, ArH), 6.96 (3H, m, ArH), 7.08 (4H, m, ArH), 7.25 (5H, m, ArH), 7.35 (1H, dd, $^3J_{HH}$ 7.6 Hz $^4J_{HH}$ 2.4 Hz, ArH), 7.49 (1H, d, $^3J_{HH}$ 5.6 Hz, ArH), 8.72 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 123.3, 126.4, 126.5, 127.1, 127.1, 127.5, 127.6, 127.7, 127.8, 129.3, 129.6, 130.3, 130.7, 131.4, 131.6, 134.9, 137.4, 137.4, 139.9, 140.2, 142.3, 142.5, 144.0, 144.6, 151.2. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 466. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{24}NS$ 466.1629, found 466.1645.

3af. Yellow wax (297 mg, 43% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 0.9 (12H, m, $CH_2CH_2CH_2CH_3$), 1.5 (16H, m, $CH_2CH_2CH_2CH_3$), 2.4 (4H, m, $CH_2CH_2CH_2CH_3$), 2.6 (4H, m, $CH_2CH_2CH_2CH_3$), 5.86 (1H, s, H, H_{alkene}), 6.44 (2H, d, $^3J_{HH}$ 10.8 Hz, ArH), 6.45 (2H, d, $^3J_{HH}$ 10.8 Hz, ArH), 6.84 (2H, d, $^3J_{HH}$ 10.8 Hz, ArH), 6.88 (2H, d, $^3J_{HH}$ 10.8 Hz, ArH), 6.98 (1H, d, $^5J_{HH}$ 2 Hz, ArH), 7.1 (5H, m, ArH), 7.21 (1H, dd, $^3J_{HH}$ 7.2 Hz, $^5J_{HH}$ 1 Hz, H_{thio}), 7.31 (1H, d, $^3J_{HH}$ 10.4 Hz, ArH), 7.54 (1H, d, $^3J_{HH}$ 7.2 Hz, H_{thio}), 8.72 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 13.9, 14.0, 14.0, 14.1, 22.1, 22.2, 22.4, 22.4, 33.4, 33.5, 33.6, 33.7, 35.2, 35.4, 110.0, 123.5, 127.0, 127.5, 127.6, 127.7, 129.1, 129.4, 130.4, 130.9, 134.7, 134.7, 135.1, 137.2, 137.7, 140.8, 141.0, 141.4, 142.0, 142.0, 144.3, 144.5, 151.5. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 690. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{49}H_{56}NS$ 690.4133, found 690.4154.

Typical Experimental Procedure for the Isoquinolines 7. The corresponding benzylamine **6** (1 mmol) and alkyne **2** (2 mmol) were added to a solution of $[Ru(p\text{-cymene})Cl_2]_2$ (0.061 g, 0.1 mmol), $[Cu(OAc)_2]$ (0.181 g, 1.0 mmol) and $K[PF_6]$ (18.7 mg, 0.1 mmol) in MeOH (3 mL) into a Young's flask. The solution was then heated at 100 °C for 24h. After that, the solvent was removed and the residue subjected to flash chromatography on neutral alumina eluting with DCM (DCM = CH_2Cl_2), then DCM/MeOH (95:5). Both eluted fractions were mixed and evaporated to dryness, affording **7** as oily materials or waxy solids, which were washed with Et_2O (10 mL) and pentane (10 mL). Compound **7fa** was further purified by a second column chromatography on silica gel eluting with mixtures hexane/ethyl acetate (9/1 to 1/1). Compounds **7la** and **7ma** were purified by column chromatography on silica gel eluting with mixtures hexane/diethyl ether (5/1 to 1/1).

7aa.[27] Waxy white solid (176 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.23 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.93 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 3.00 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 7.43 (1H, td, $^3J_{HH}$ 7.6 Hz $^4J_{HH}$ 0.8 Hz, ArH), 7.62 (1H, ddd, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.62 (1H, ddd, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 7.6 Hz $^4J_{HH}$ 1.2 Hz, ArH), 7.83 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.90 (1H, dd, $^3J_{HH}$ 8.4 Hz, $^4J_{HH}$ 0.8 Hz, ArH), 9.01 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.7, 15.1, 20.1, 122.8, 125.6, 127.3, 128.2, 129.0, 130.0, 135.1, 150.2, 153.8. $(ESI)^+$ *m/z*: $[M]^+$ (100) 186. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{16}N$ 186.1283, found 186.1276.

7ba. Yellow oil (205 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.17 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.23 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.85 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.88 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 3.81 (3H, s, OCH_3), 7.00 (1H, dd, $^3J_{HH}$ 8.8 Hz, $^4J_{HH}$ 2.4 Hz, ArH), 7.43 (1H, d, $^4J_{HH}$ 2.0 Hz, ArH), 7.62 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 8.82 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.5, 14.6, 20.9, 28..4, 55.3, 101.0, 118.2, 123.1, 128.0, 129.9, 136.8, 149.3, 154.1, 160.8. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 216. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}NO$ 216.1388, found 216.1383.

7ca. Waxy white solid (229 mg, 93% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.15 (3H, t, $^3J_{HH}$ 7.5 Hz, CH_2CH_3), 1.23 (3H, t, $^3J_{HH}$ 7.3 Hz, CH_2CH_3), 2.88 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 3.14 (2H, q, $^3J_{HH}$ 7.2 Hz, CH_2CH_3), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.53 (1H, d, $^4J_{HH}$ 2.4 Hz, ArH), 6.64 (1H, d, $^4J_{HH}$ 2.4 Hz, ArH), 8.78 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.8, 16.0, 23.4, 28.2, 55.3, 55.5, 97.7, 102.3, 124.0, 130.1, 130.2, 148.5, 153.2, 157.6, 157.7. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 246. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$ 246.1494, found 246.1506.

7da. Waxy white solid (190 mg, 88% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.19 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.26 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.91 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.94 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 3.90 (3H, s, OCH_3), 6.70 (1H, d, $^3J_{HH}$ 7.3 Hz, ArH), 7.43 (1H, t, $^3J_{HH}$ 7.6 Hz, ArH), 7.46 (1H, d, $^3J_{HH}$ 7.6 Hz, ArH), 9.39 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.7, 15.0, 21.1, 28.4, 55.6, 103.6, 114.9, 119.4, 128.5, 130.4, 136.4, 145.1, 154.4, 157.0. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 216. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}NO$ 216.1388, found 216.1390.

7ea. Waxy white solid (187 mg, 76% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.18 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.26 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.86 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.91 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 3.89 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 7.04 (1H, s, ArH), 7.06 (1H, s, ArH), 8.78 (1H, s, CHN) (signals due to the major isomer). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.6, 14.7, 55.9, 101.2, 105.8, 123.3, 127.9, 131.5, 147.6, 149.1, 152.6, 152.7 (signals due to the major isomer). $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 246. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$ 246.1494, found 246.1489.

7fa. Orange oil (142 mg, 43% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.26 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.32 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.99 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 3.09 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 8.02 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 8.21 (1H, dd, $^3J_{HH}$ 8.8 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 8.71 (1H, d, $^4J_{HH}$ 2.0 Hz, ArH), 9.17 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.4, 15.4, 21.0, 28.4, 119.2, 119.7, 128.7, 130.3, 131.0, 134.4, 142.0, 150.1, 156.3. $(ESI)^+$ *m/z*: $[M + H]^+$ (50) 231. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{15}N_2O_2$ 231.1134, found 231.1128.

7ga.[28] Yellow oil (116 mg, 58% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.20 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.25 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.83 (3H, s, CH_3), 2.87 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.89 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 7.40 (1H, ddd, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 6.8 Hz, $^4J_{HH}$ 1.4 Hz, ArH), 7.56 (1H, ddd, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 6.8 Hz, $^4J_{HH}$ 1.4 Hz, ArH), 7.88 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.46 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 15.0, 15.3, 20.7, 22.4, 28.5, 123.3, 125.3, 126.1, 126.2, 127.2, 129.5, 135.1, 152.6, 155.8. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 200. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}N$ 200.1439, found 200.1434.

7ha. Yellow oil (150 mg, 68% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.19 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.26 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.91 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.93 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 7.36(1H, dd, $^3J_{HH}$ 8.7 Hz, $^4J_{HH}$ 1.9 Hz, ArH), 7.75 (1H, d, $^3J_{HH}$ 8.7 Hz, ArH), 7.85(1H, d, $^4J_{HH}$ 1.9 Hz, ArH), 9.05 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 13.5, 13.9, 19.8, 27.3, 121.0, 124.4, 125.7, 127.3, 128.8, 134.9, 135.4, 148.8, 153.9. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 220. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{15}ClN$ 220.0893, found 220.0888.

7ia. Yellow oil (178 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.22 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.95 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 3.03 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 7.60 (1H, dd, $^3J_{HH}$ 8.8 Hz, $^4J_{HH}$ 1.6 Hz, ArH), 7.96 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 8.19 (1H, s, ArH), 9.08 (1H, s, CHN). δ_F: −62.71. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.5, 15.1, 20.8, 28.4, 120.7 (q, $^4J_{CF}$ 18 Hz), 121.4 (q, $^1J_{CF}$ 1084 Hz), 127.4, 129.4, 129.9, 131.6 (q, $^2J_{CF}$ 124 Hz), 134.2, 150.1, 155.5. $(ESI)^+$ *m/z*: $[M + H]^+$ (100) 254. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{15}F_3N$ 254.1157, found 254.1151.

7ja. Waxy white solid (182 mg, 91% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.24 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.50 (3H, s, CH_3), 2.92 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.98 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 7.28 (1H, dd, $^3J_{HH}$ 8.3 Hz, $^4J_{HH}$ 1.3 Hz, ArH), 7.67 (1H, s, ArH), 7.75 (1H, d, $^3J_{HH}$ 8.3 Hz, ArH), 8.95 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.7, 15.0, 20.7,

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22.5, 28.3, 121.8, 125.7, 127.9, 128.1, 128.5, 135.3, 140.2, 149.8, 153.8. (ESI)$^+$ *m/z*: [M + H]$^+$ (100) 200. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{14}H_{18}N$ 200.1439, found 200.1434.

7ka. Waxy white solid (198 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.24 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ 7.6 Hz,) CH_2CH_3, 1.36 (9H, s, $C(CH_3)_3$), 2.92 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 3.02 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 7.53 (1H, dd, $^3J_{HH}$ 8.8 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 7.78 (1H, d, $^3J_{HH}$ 8.8 Hz, ArH), 7.83 (1H, d, $^3J_{HH}$ 0.8 Hz, ArH), 8.95 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.7, 15.0, 20.8, 28.4, 31.2, 34.5, 117.7, 124.6, 125.7, 127.2, 129.0, 135.0, 149.6, 153.0, 153.8. (ESI)$^+$ *m/z*: [M + H]$^+$ (100) 242. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{24}N$ 242.1909, found 242.1916.

7la. Yellow oil (201 mg, 85% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.20 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.29 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.94 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.97 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 7.45 (1H, td, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.56 (1H, td, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.73 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.74 (2H, s, ArH), 8.61 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 9.76 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.6, 15.6, 21.1, 28.5, 121.2, 121.9, 123.2, 126.9, 127.7, 128.6, 130.0, 130.2, 131.1, 131.2, 134.6, 144.2, 156.1. (ESI)$^+$ *m/z*: [M + H]$^+$ (100) 236. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{18}N$ 236.1439, found 236.1434.

7ma. Waxy white solid (226 mg, 91% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.26 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.88 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 2.94 (3H, s, CH_3), 3.04 (2H, q, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 7.36 (1H, td, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.41 (1H, td, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.88 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.90 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 8.34 (1H, s, ArH), 8.54 (1H, s, ArH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 14.9, 15.2, 20.9, 22.8, 28.4, 121.7, 125.0, 125.6, 125.9, 126.0, 127.0, 128.2, 128.8, 130.8, 130.9, 132.0, 133.8, 149.9, 157.5. (ESI)$^+$ *m/z*: [M + H]$^+$ (100) 250. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{18}H_{20}N$ 250.1596, found 250.1590.

7ab (Both Isomers). Yellow oil (143 mg, 77% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 0.95 (3H, t, $^3J_{HH}$ 7.6 Hz, CH_2CH_3), 1.70 (2H, m, CH_3CH_2), 2.53 (3H, s, CH_3), 2.92 (2H, m, $CH_3CH_2CH_2$), 7.36 (1H, td, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.41 (1H, ddd, $^3J_{HH}$ 9.2 Hz, $^3J_{HH}$ 6.8 Hz $^4J_{HH}$ 1.2 Hz, ArH), 7.61 (1H, ddd, $^3J_{HH}$ 9.2 Hz, $^3J_{HH}$ 6.8 Hz $^4J_{HH}$ 1.2 Hz, ArH), 7.83 (1H, d, $^3J_{HH}$ 9.2 Hz, ArH), 7.90 (1H, dq, $^3J_{HH}$ 8.8 Hz $^4J_{HH}$ 0.8 Hz, ArH), 9.00 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 13.2, 22.2, 29.3, 36.9, 121.9, 122.3, 124.7, 125.9, 127.0, 128.9, 134.9, 148.8, 152.0. (ESI)$^+$ *m/z*: [M + H]$^+$ (40) 186. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{13}H_{16}N$ 186.1283, found 186.1269.

7ac. Waxy white solid (185 mg, 93% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.49 (9H, s, $C(CH_3)_3$), 2.72 (3H, s, CH_3), 7.41 (1H, ddd, $^3J_{HH}$ 8.0 Hz, $^3J_{HH}$ 6.8 Hz $^4J_{HH}$ 1.2 Hz, ArH), 7.61 (1H, ddd, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 6.8 Hz $^4J_{HH}$ 1.6 Hz, ArH), 7.82 (1H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.93 (1H, dq, $^3J_{HH}$ 8.4 Hz $^4J_{HH}$ 0.8 Hz, ArH), 9.00 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 16.2, 31.0, 38.6, 122.9, 123.8, 125.8, 126.7, 127.7, 129.7, 137.1, 148.3, 158.7. (ESI)$^+$ *m/z*: [M + H]$^+$ (100) 200. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{14}H_{18}N$ 200.1439, found 200.1434.

7ad. Yellow oil (139 mg, 41% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 1.72 (3H, d, $^3J_{HH}$ 1.2 Hz, CH_3), 2.38 (3H, s, CH_3), 6.31 (1H, m, H_{alkene}), 6.94 (2H, d, $^3J_{HH}$ 8.0 Hz, ArH), 7.14 (2H, t, $^3J_{HH}$ 8.0 Hz, ArH), 7.35 (5H, m, ArH), 7.54 (1H, ddd, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.66 (1H, ddd, $^3J_{HH}$ 8.4 Hz, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.92 (2H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 4.0 Hz, ArH), 9.12 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 15.3, 19.2, 123.5, 123.6, 124.9, 126.2, 126.4, 126.6, 126.9, 127.3, 127.9, 128.0, 128.1, 128.3, 129.6, 130.3, 130.3, 130.4, 138.1, 145.4, 149.8. (ESI)$^+$ *m/z*: [M + H]$^+$ (100) 336. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{25}H_{22}N$ 336.1752, found 336.1752.

7ae. Orange oil (242 mg, 53% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.06 (1H, s, H_{alkene}), 6.44 (2H, d, $^3J_{HH}$ 6.7 Hz, ArH), 6.75 (2H, d, $^3J_{HH}$ 7.6 Hz, ArH), 6.81 (2H, d, $^3J_{HH}$ 7.6 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 6.88 (1H, t, $^3J_{HH}$ 7.6 Hz, ArH), 7.0–7.3 (10H, m, ArH), 7.4–7.6 (3H, m, ArH), 7.8 (1H, m, ArH), 8.84 (1H, s, CHN). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C: 125.9, 126.5, 126.7, 126.9, 127.1, 127.2, 127.4, 127.5, 127.7, 127.8, 129.2, 129.8, 130.1, 130.2, 130.5, 131.0, 131.5, 131.6, 135.1, 136.5, 137.4, 140.2, 140.4, 142.6, 143.9, 150.8, 151.3. (ESI)$^+$ *m/z*: [M + H]$^+$ (100) 460. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{35}H_{26}N$ 460.2060, found 460.2068.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all prepared compounds. In situ NMR experiments. NOE spectrum of **3ac**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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