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Recent Advances in the Synthesis of Azonia Aromatic Heterocycles

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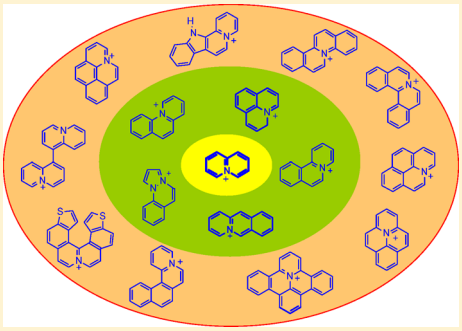
ABSTRACT: Azonia aromatic heterocycles are an important subclass of aza-heterocyles as they are the structural motif of relevant cationic alkaloids, and they have a wide range of potential applications such as bioactive compounds and organic materials. In this Synopsis, recent and novel approaches to their synthesis are surveyed, with particular emphasis on ring-closing metathesis reactions and annulation reactions based on C−H activation.



It is difficult to find in the literature a general name to refer in a simple way to all charged aromatic heterocycles in which

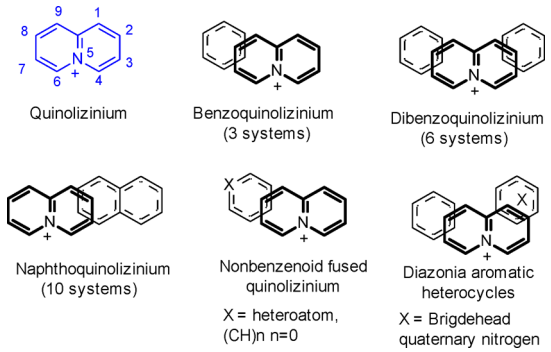


Figure 1. General structures of representative AZAH systems.

the cationic structure is produced by the presence of a quaternary bridgehead nitrogen. Here, we use the term "*azonia aromatic heterocycles*" (AZAHs) to include any fully aromatic heterocycle that contains at least one quaternary nitrogen in a bridgehead position.[1]

The simplest and most representative example of this kind of heterocycle is the pyrido[1,2-*a*]pyridinium system, which is known by the trivial name quinolizinium. There are three isomeric benzo-, six dibenzo-, and 10 naphthoquinolizinium structures and 83 pentacyclic quinolizinium-based systems.[2] Non-benzenoid-fused quinolizinium derivatives and diazonia aromatic heterocycles (DAZAH) are also relevant members of this class of heterocycle (Figure 1).

Quinolizinium, as a charged moiety or as a quinolizinium ylide, is present in the structures of relevant natural alkaloids such as coralyne, the berberine family (more than 60 alkaloids), sempervirine, flavopereirine, afrocurarine, neooxygambirtannine, and flavocarpine (inter alia). Furthermore, AZAH derivatives have a wide range of potential applications such as bioactive compounds, fluorescent dyes, DNA intercalators, ionic liquids, and organic materials.[3] The aim of this Synopsis is to survey the recent advances in the synthesis of AZAH systems. These methods are categorized on the basis of reaction types employed to build up the heterocycle, and they include the following: (1) ring-closing metathesis (RCM) reactions, (2) annulation reactions based on C−H activation, and (3) other recent and novel approaches to AZAH systems.

From the synthetic point of view, there are two main approaches to the syntheses of the parent AZAH and its derivatives. One route is based on the use of an azine as starting material and involves the formation of a N−C bond in a cyclization reaction. The other route has an azinium or azolium salt as a precursor, and this involves the formation of a C−C bond by a cyclization process or the formation of two C−C bonds in condensation reactions. These different approaches employed for the quinolizinium system were also adapted for the synthesis of polycyclic heterocycles.

All of the syntheses for quinolizinium salts based on classical cyclization strategies and conditions, including the first synthesis of quinolizinium itself,[4] were first reviewed by Thyagarajan.[5] Jones[6] published a review that covered the chemistry of quinolizinium and its benzo derivatives, and a more recent review focused on the chemistry of these cationic heterocycles, with an updated version published by Ihmels.[7] A brief overview was reported by us in a chapter of *Modern Heterocyclic Chemistry*.[8] However, to date, the only general survey that covers quinolizinium and polycyclic aromatic nitrogen cations[9] was published by Arai and Hida in 1992.

Ring-Closing Metathesis Reactions. In the pioneering work of Grubbs and Fu,[10] it was demonstrated how a RCM reaction can be applied to the synthesis of heterocycles, and this opened one of the most relevant cyclization strategies to prepare a wide variety of heterocyclic systems under very mild

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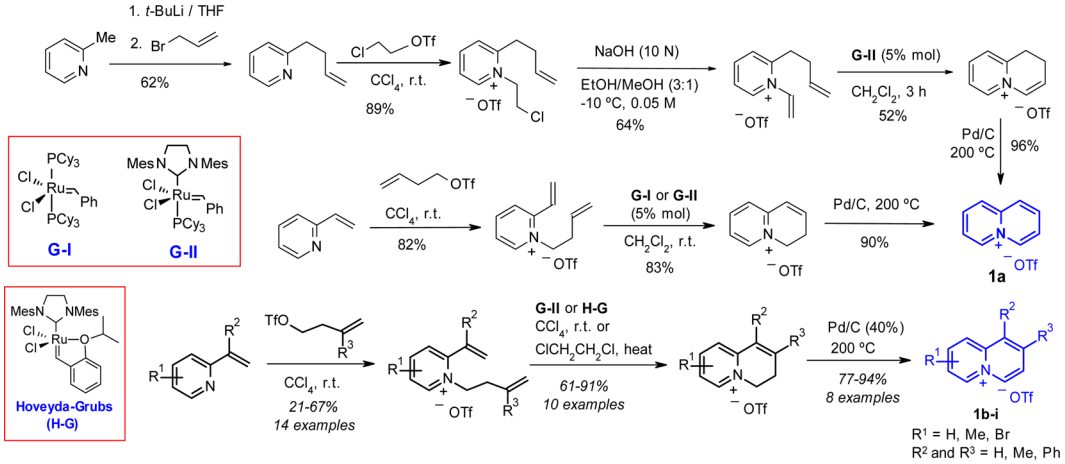
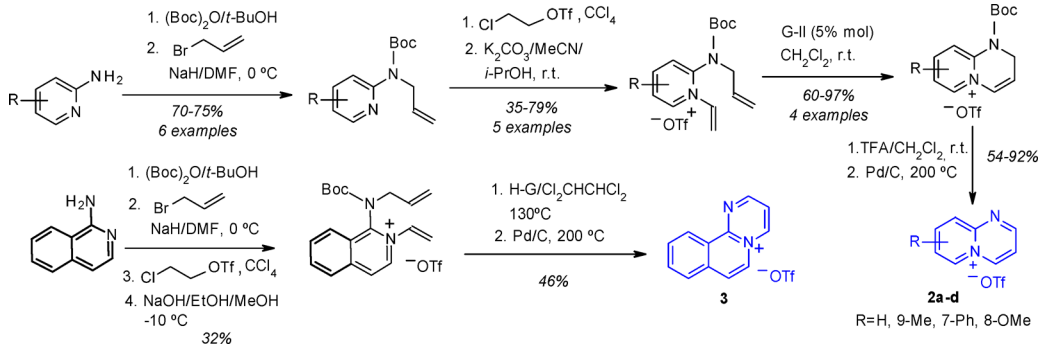
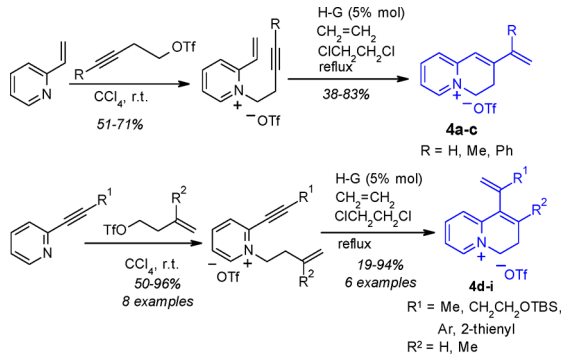
Scheme 1. Synthesis of Quinolizinium Triflate and Quinolizinium Derivatives by RCM



Scheme 2. Synthesis of 1-Azaquinolizinium Derivatives 2 and Pyrimido[2,1-*a*]isoquinolinium Triflate 3



Scheme 3. Synthesis of Alkenyl-Substituted 3,4-Dihydroquinolizinium Triflates 4



conditions.[11] The quinolizinium system (**1a**) and other AZAHs were obtained by us in a RCM process involving the formation of β and δ bonds with respect to the nitrogen atom of the azinium substrate[12] using first (G-I) and/or second (G-II) generation Grubbs catalysts in the metathesis reactions.[13] In a comparative study, the approach from *N*-(3-butenyl)-2-vinylpyridinium (C1−C2 bond formation) afforded the quinolizinium triflate in 54% overall yield, whereas the strategy based on the C3−C4 bond disconnection gave **1a** in only 18% overall yield[14] (Scheme 1).

The former approach was chosen to study the scope of the RCM reaction from dienic pyridinium salts as a general method for the synthesis of substituted 3,4-dihydroquinolizinium salts and the corresponding quinolizinium derivatives after oxidation. The presence of substituents(s) on the pyridine ring and on the vinyl and/or butenyl moieties allowed the synthesis of differently substituted 3,4-dihydroquinolizinium triflates using G-II or Hoveyda−Grubbs (H-G) catalysts for the metathesis reaction.[13,15] Most of these salts could be oxidized to the corresponding quinolizinium derivatives under conditions similar to those employed for **1a** (Scheme 1).

The strategy based on the cyclization reaction of 2-butenyl-*N*-vinyl was the only feasible approach that could be adapted for the synthesis of a quinolizinium system bearing an extra nitrogen heteroatom. Thus, the formation of the bicyclic pyrido[1,2-*a*]pyrimidin-5-ium (1-azaquinolizinium) system (**2a**)[16] was achieved by a RCM reaction of the *N*-Boc-protected *N*-vinyl-2-propenylamino dienes using the G-II catalyst.[17] Several simple 1-azaquinolizinium derivatives **2b−d** were also obtained from the corresponding azadienes (Scheme 2). This approach was also successfully applied to the first reported synthesis of the pyrimido[2,1-*a*]isoquinolinium (benzo-1-azaquinolizinium) compound **3** by using the Hoveyda−Grubbs catalyst in the RCM reaction (Scheme 2).

In an effort to develop a route to benzoquinolizinium systems, a tandem enyne RCM/Diels−Alder reaction was designed. Although the overall process was unsuccessful, a new approach to 1- and 2-vinyl-substituted 3,4-dihydroquinolizinium cations **4a−i** by a ring-closing enyne metathesis (RCEYM)[18] reaction on appropriately substituted pyridinium substrates was reported[19] (Scheme 3).

Enynes resulting from the *N*-alkylation of 2-alkynylpyridines with 3-alkenyl triflates gave the RCM reaction under similar conditions to afford 1-alkenyl-substituted 3,4-dihydroquinolizi-

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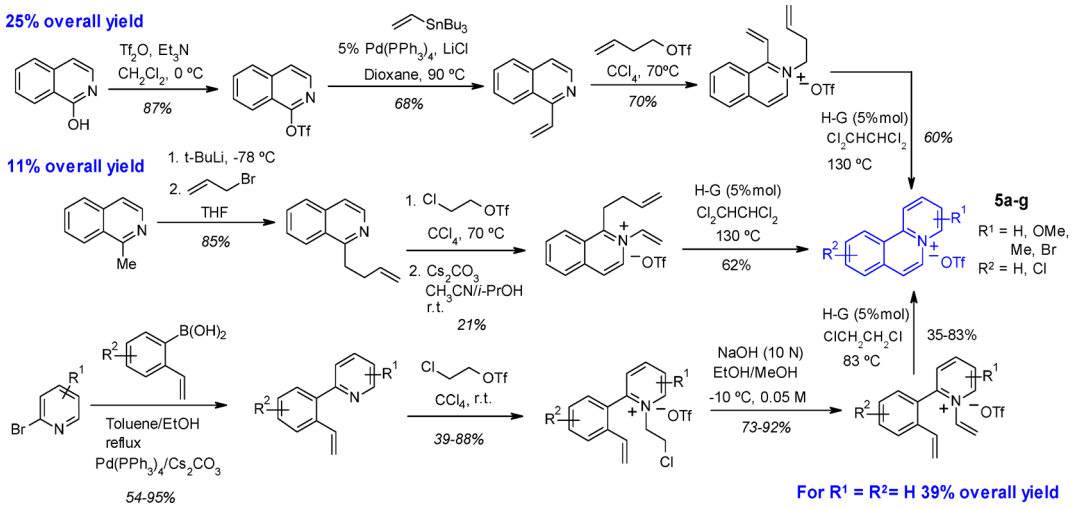
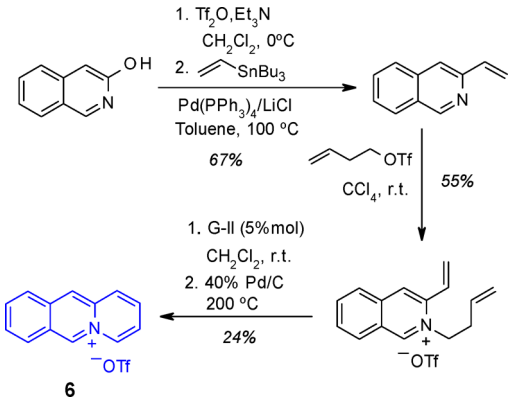
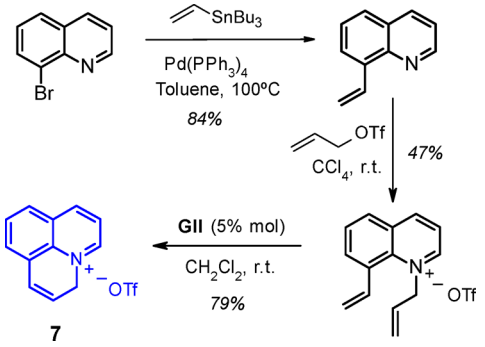
Scheme 4. Synthesis of Benzo[*a*]quinolizinium Derivatives



Scheme 5. Synthesis of the Benzo[*b*]quinolizinium System 6



Scheme 6. Synthesis of 3*H*-Pyrido[3,2,1-*ij*]quinolinium Triflate (7)



nium salts (**4d–i**) in good isolated yields (Scheme 3). Substitution on the alkenyl moiety had a significant influence on the yield of the reaction, and 1,2-disubstituted quinolizinium derivatives were obtained in low yields. The results of some experiments indicate that the metathesis is probably initiated on the alkene for the formation of **4a–c** and in the alkynyl moiety for **4d–i**, with the role of ethylene being to promote the formation of the active methylidene ruthenium complex.

Benzo[*a*]quinolizinium was synthesized by classical cyclization methods involving the formation of C4–N5,[20] C6–C7,[21] and C1a–C11a[22] bonds from pyridine and isoquinoline as starting heterocycles. Our approaches based on a key RCM reaction involved C1–C2, C3–C4, and C6–C7 bond formation.[23] The first two strategies are similar to those employed to build the quinolizinum system, whereas the third can only be applied to this system or other polycyclic aromatic heterocycles with similar ring fusion.[24] Our results confirmed that under optimized conditions the strategy involving the formation of the C6–C7 bond of the tricyclic system afforded better overall yields than strategies based on the formation of C1–C2 or C3–C4 bonds (39% *vs* 25% and 11%, respectively). The most efficient method was applied to the synthesis of several unknown benzo[*a*]quinolizinium derivatives **5a–g** (Scheme 4).

Benzo[*b*]quinolizinium (acridizinium) bromide was prepared for the first time through a cyclization reaction involving C10a–C11 bond formation.[25] Two improved procedures also involved the formation of this bond,[26] and a more recent synthetic method led to this system through N5–C6 bond formation.[27]

We explored both C1–C2 and C3–C4 bond formation, and it was found that the RCM reaction produced the 3,4-dihydrobenzo[*b*]quinolizinium in good yield; however, the oxidation reaction gave only a moderate yield of the triflate salt **6**[13,15] (Scheme 5). On the other hand, all of our attempts to obtain the appropriate diene for C1–C2 bond formation were unsuccessful, probably due to the low stability of the isoquinolinium diene.

A similar strategy was used for the first preparation of the 3*H*-pyrido[3,2,1-*ij*]quinolinium triflate (**7**) in 32% overall yield[15] (Scheme 6).

We also demonstrated that the most efficient procedure developed for the synthesis of the benzo[*a*]quinolizinium system could be easily adapted to the preparation of some representative examples of dibenzo- and naphthoquinolizinium systems. Thus, dibenzo[*a,f*]quinolizinium and dibenzo[*a,h*]-quinolizinium triflates **8a** and **9a** were obtained from the appropriate quinolinium and isoquinolinium dienes[24] (Scheme 7).

Analogously, the naphtho[1,2-*a*]quinolizinium system (**10**) was obtained by the synthetic route shown in Scheme 8.[24]

Another example of the utility of the RCM reaction in AZAH synthesis is the preparation of a non-benzenoid quinolizinium derivative, the indolo[2,3-*a*]quinolizinium alkaloid **11**, by two synthetic routes involving the formation of the C1–C2 and

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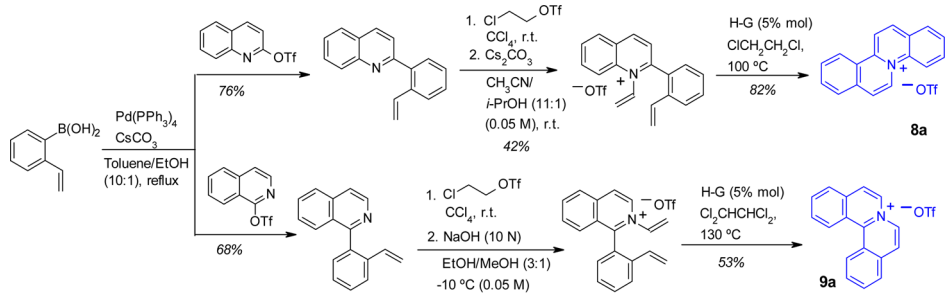
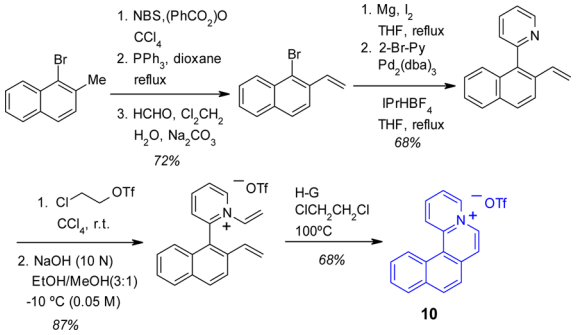
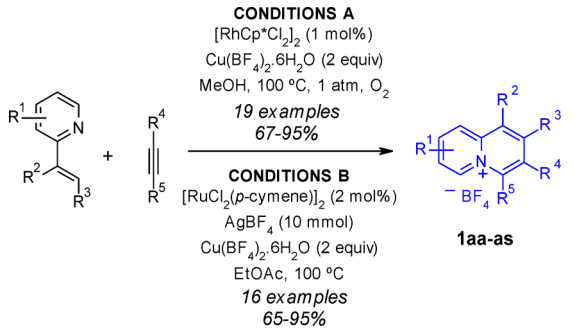
Scheme 7. Synthesis of Dibenzo[*a,f*]quinolizinium (8a) and Dibenzo[*a,h*]quinolizinium (9a) Salts



Scheme 8. Synthesis of Naphtho[1,2-*a*]quinolizinium Triflate (10)



Scheme 10. Synthesis of Quinolizinium Salts by Rh(III)- or Rh(II)-Catalyzed C−H Bond Activation of 2-Alkenylpyridines



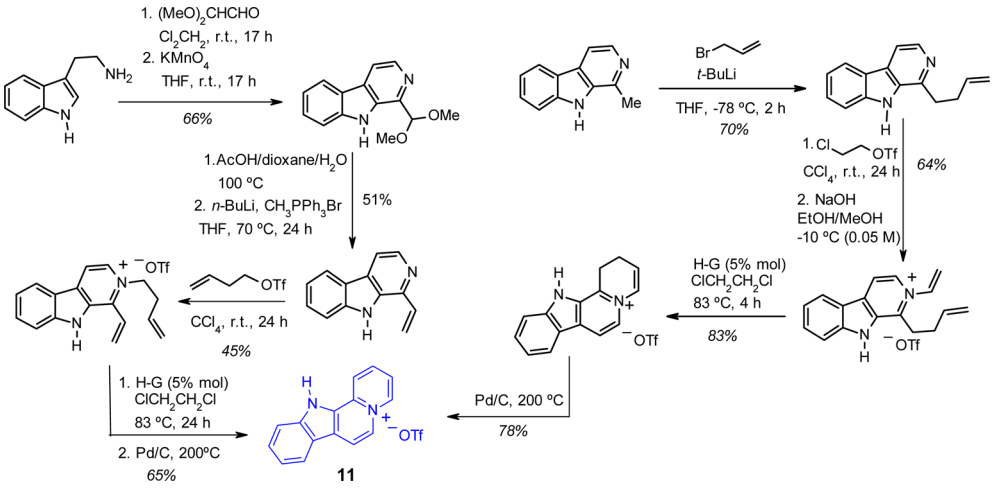
R1, R2, R3, R4 and R5 = H, Alkyl, OMe, CO_2Et, Ar, 2-thienyl

C3−C4 bonds for the construction of the quinolizinium core.[28] The best approach provided the tetracyclic cation in only five steps from commercially available harmane in 36% overall yield[29] (Scheme 9).

Annulation Reactions Based on C−H Activation. Cheng and co-workers reported a very efficient approach for di-, tri-, and tetrasubstituted quinolizinium tetrafluoroborates involving the formation of C2−C3 and C4−N5 bonds by the reaction of 2-vinylpyridines and alkynes by Rh(III)- or Ru(II)-catalyzed C−H activation and annulation.[30] The reactions were conducted in the presence of 1 mol % of $[RhCp^*Cl_2]_2$ and 0.5 equiv of $Cu(BF_4)_2{\cdot}6H_2O$ in MeOH at 60 °C under an O_2 atmosphere or using $[RuCl_2(p\text{-cymene})]_2$ (2 mol %) as the catalyst in the presence of $Cu(BF_4)_2{\cdot}6H_2O/AgBF_4$ in EtOAc at 100 °C (Scheme 10). The results indicate that in some cases the Rh catalyst is more active than the corresponding Ru one, but the two catalysts showed some complementary reactivity in the formation of the quinolizinium system.

In the same year, Huang and co-workers developed a similar rhodium-catalyzed method for the synthesis of benzo[*a*]-quinolizinium salts (**5aa−ar**) based on the reaction of arenes and alkynes by oxidative C−H bond activation and annulation.[31] The method also allowed the synthesis of other AZAHs, such as dibenzo[*af*]quinolizinium (**8b**), pyrazolo[1,2-*a*]cinnolin-4-ium (**12**), and naphtho[2,1,8-*ija*]quinolizinium (**13**). Mechanistic studies confirmed the easy oxidation of Rh(I) to Rh(III) by molecular oxygen facilitated by acids, and

Scheme 9. Synthesis of Indolo[2,3-*a*]quinolizinium Triflate (11)



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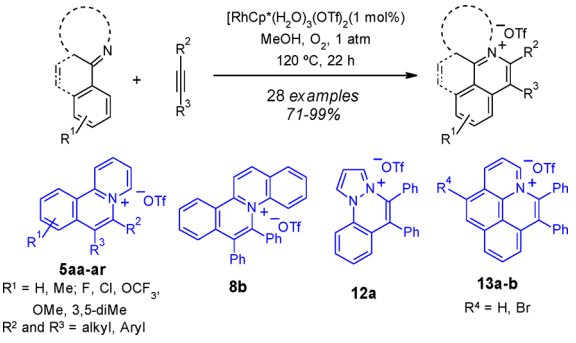
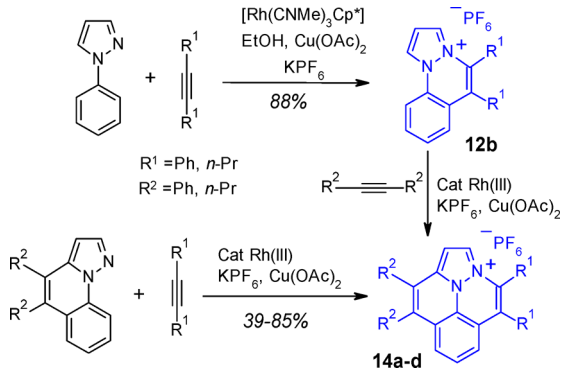
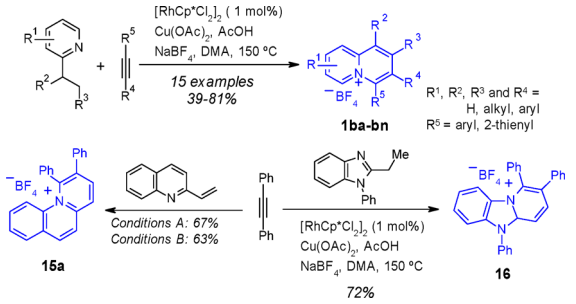
Scheme 11. Synthesis of Benzo-, Dibenzo-, Pyrazolo-, and Naphthoquinolizinium Salts



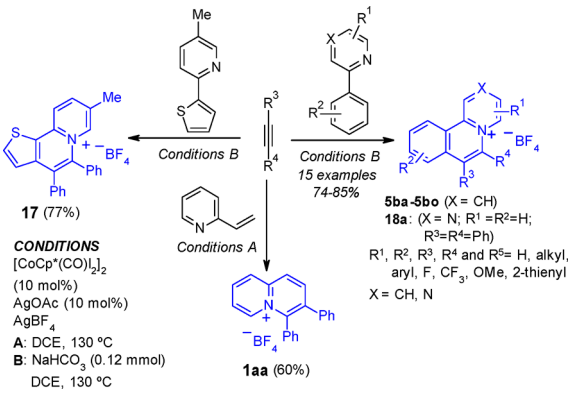
Scheme 12. Synthesis of Pyrazolo[1,2-*a*]cinnolin-4-ium and 9b-Aza-2a-azoniacyclopenta[*cd*]phenalene Systems



Scheme 13. Synthesis of Quinolizinium, Benzo[c]quinolizinium and Pyrido[1,2-*a*]benzimidazolium Salts by Cooperative C(sp^3)−H and C(sp^2)−H Activation



Scheme 14. Synthesis of Benzo- and Thienoquinolizinium and Pyrazino[2,1-*a*]isoquinolin-5-ium Salts



this led to the isolation and characterization of rhodium complexes (Scheme 11).

An elegant mechanistic study of the reaction of 1-phenylpyrazole, 2-phenylpyridine, and 2-vinylpyridine with diphenylacetylene and 4-octyne was reported by Davies and Macgregor.[32] It was shown the reaction proceeded via initial C−H activation, alkyne insertion, and reductive coupling. Experimental results and computational studies have shown how these reactions can be affected by the type of substrate involved and the reaction conditions. 1-Phenylpyrazole was the only substrate able to form tetracyclic cationic compounds by reacting with 2 equiv of the alkyne. Moreover, the reaction is very sensitive to the solvent, producing C−C or C−N coupling depending on the solvent used. Thus, in EtOH pyrazolo[1,2-*a*]cinnolin-4-ium, **12b** was formed in contrast to the C−C coupling processes observed in xylene.[33] Compound **12b** was the precursor of 9b-aza-2a-azoniacyclopenta[*cd*]phenalene **14b**, which in turn could also be obtained from the alternative C−C coupled substrate (Scheme 12).

More recently, Cheng and co-workers reported a novel [4 + 2] approach to the quinolizinium system based on the use of 2-ethylpyridines instead of 2-alkenylpyridines.[34] In this case, the formation of the quinolizinium system was achieved by using 1 mol % of a Rh(III) catalyst along with an excess of a copper(II) salt (Scheme 13). Both methods were employed for the synthesis of two tricyclic systems, namely, the 1,2-diphenylbenzo[*c*]quinolizinium[35] (**15a**) from the reaction of diphenylacetylene and 2-vinylquinoline and the 1,2,5-triphenylpyrido[1,2-*a*]benzimidazolium (**16**) from the same alkyne and 2-ethyl-1-phenylbenzimidazole[32] (Scheme 13). A series of mechanistic studies with 2-alkyl- and 2-alkenylpyridines and diphenylacetylene[36] allowed to establish the catalytic cycle for the formation of the quinolizinium salt.

In another example of the utility of this strategy for the synthesis of AZAHs and azinium salts, Cheng and co-workers reported a successful cobalt-catalyzed oxidative annulation of 2-vinylpyridines and 2-aryl- and 2-heteroarylazines with alkynes.[37] The reactions led to the formation of the corresponding quinolizinium (**1aa**), benzo[*a*]quinolizinium (**5ba−bo**), thieno-[2,3-*a*]quinolizinium (**17**), and pyrazino[2,1-*a*]isoquinolin-5-ium (**18a**) salts in yields of up to 74% (Scheme 14).

Choudhury and Ghorai recently demonstrated very interesting behavior of *N*-heterocyclic carbenes (NHC) as directing groups in aromatic C−H activation. This phenomenon allowed the synthesis of imidazo[1,2-*a*]quinolinium and benzoimidazo-[1,2-*a*]quinolinium systems (**19a−p**) from imidazolium and benzoimidazolium salts and alkynes under mild conditions[38] (Scheme 15). Initial studies and the isolation and full characterization of the NHC-cyclometalated rhodium(III) intermediate suggested that the formation of the tricyclic system involved NHC-directed C−H activation/insertion/annulative reductive elimination/oxidative catalyst regeneration.

In an extension of their work on the Rh(III)-catalyzed C−H activation/annulation, the Choudhury group described a rhodium(III)-catalyzed cascade double aromatic C−H activation/annulation to synthesize a variety of polycyclic heteroaromatic molecules, some of which contained the benzo[*ij*]-imidazo[2,1,5-*de*]quinolizinium system[39] (**20a−l**) (Scheme 15). The method relies on unprecedented sequential *normal* and *abnormal* C−H activations under rhodium(III) oxidative catalysis.

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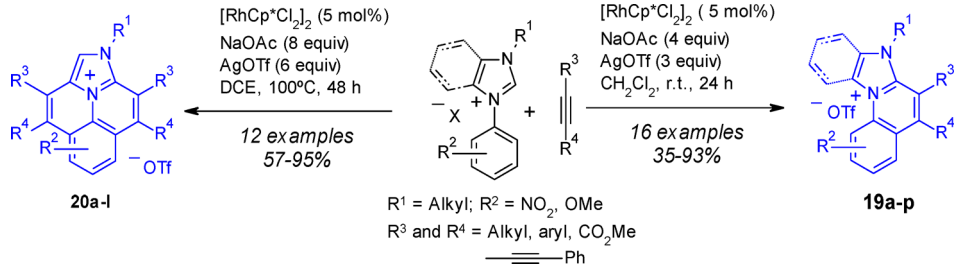
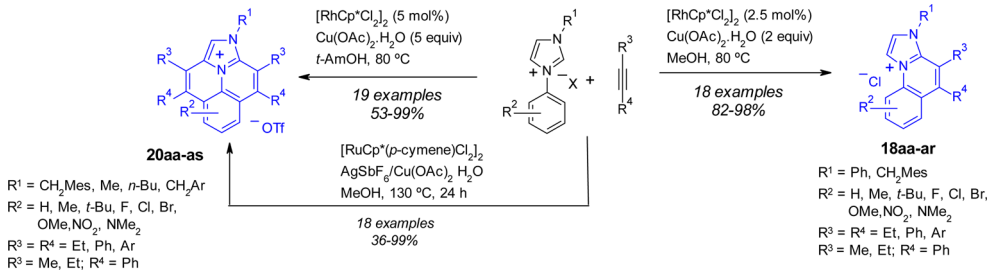
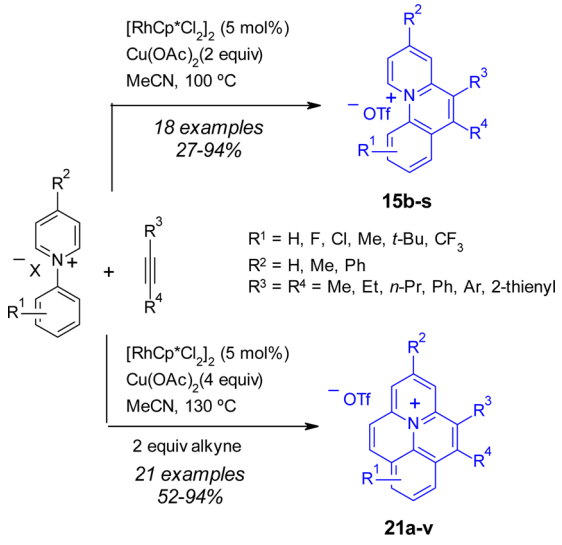
Scheme 15. Synthesis of Imidazo[1,2-*a*]quinolinium, Benzoimidazo[1,2-*a*]quinolinium, and Benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium Salts



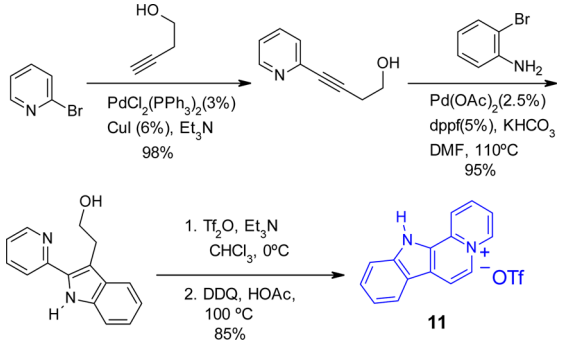
Scheme 16. Synthesis of Azoloquinolinium Salts



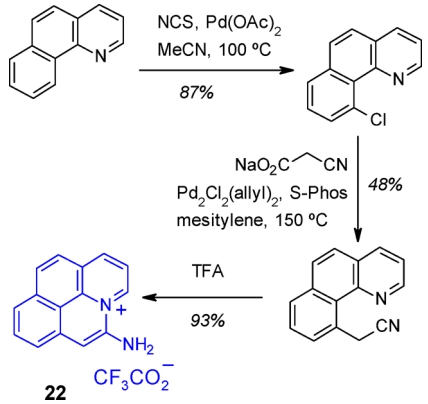
Scheme 17. Synthesis of Benzo[*c*]- and Benzo[*ij*]pyrido[2,1,6-*de*]quinolizinium Salts



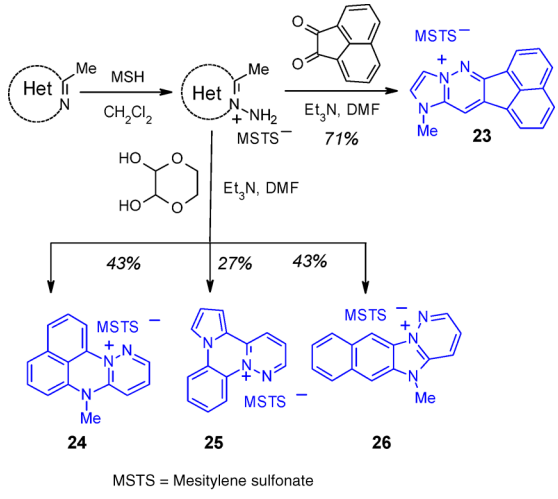
Scheme 18. Synthesis of Indoloquinolizinium Alkaloids



Scheme 19. Synthesis of 5-Aminonaphtho[2,1,8-*ija*]quinolizinium Triflate



Scheme 20. Synthesis of Perimidinium, Quinoxalinium, and Pyridazinium Salts



Further studies using substrates containing the imidazolium system and pyridine in chelating fashion showed a bimodal C–

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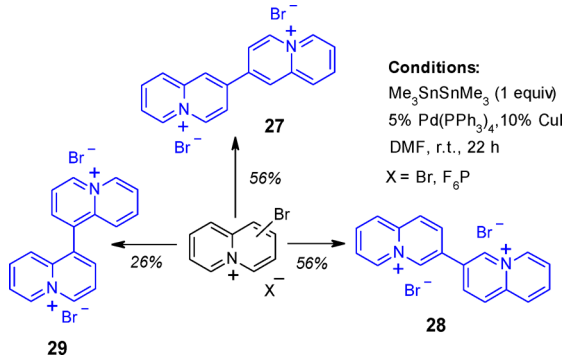
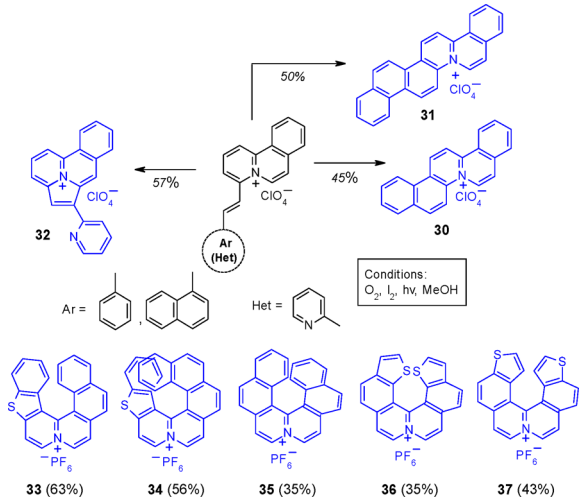
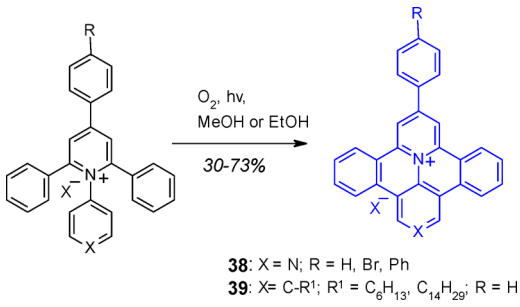
Scheme 21. Synthesis of Biquinolizinium Cations



Scheme 22. Synthesis of Polycyclic AZAHs by Oxidative Photocyclizations



Scheme 23. Synthesis of Quinolizino Naphthyridinium and Phenanthridinium Salts by Oxidative Photocyclization



H activation−functionalization with both electronic and steric factors playing a key role in achieving the annulation reaction. Several mechanistic studies suggested the nature of the activation mechanism, highlighting an important pyridine coordination effect during the catalysis.[40]

Wang and co-workers also explored the reactivity of aryl imidazolium salts with alkynes under conditions similar to those reported by Choudhury. Their results showed that these reactions also proceed efficiently and in a highly regioselective manner in the presence of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2{\cdot}H_2O$ to give the corresponding substituted imidazo[1,2-*a*]quinolinium and benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium salts[41] (**19aa−ar**) (Scheme 16). Studies conducted in order to gain an insight into the mechanism of this reaction allowed the isolation and full characterization of both rhodacyclic intermediates, which were transformed into the corresponding tricyclic and tetracyclic aromatic cations by reaction with diphenylacetylene.

In a subsequent study, the bis-annulated benzo[*ij*]imidazo-[2,1,5-*de*]quinolizinium salts (**20aa−as**) were also obtained in moderate to good yields using a Ru(II) catalyst.[42] The reactions proceeded with good regioselectivity, and mono-annulated products could be obtained by reducing the amount of ruthenium catalyst (Scheme 16).

The same authors also reported an efficient Rh(III)-catalyzed reaction of arylpyridiniums with alkynes to afford highly substituted benzo[*c*]quinolizinium (**5b−o**) and benzo[*ij*]-pyrido[2,1,6-*de*]quinolizinium (**21a−v**) salts via rhodium(III)-catalyzed multiple C−H activation annulation reactions in a one-pot process[43] (Scheme 17).

Other Recent and Novel Approaches to AZAH. The 12*H*-indolo[2,3-*a*]quinolizin-5-ium (**11**) was also synthesized in a cyclization reaction that involves the formation of the C6−C7 bond.[44] Thus, consecutive Sonagashira coupling and Larock indole annulation reactions allowed the efficient synthesis of a pyridylindole derivative, which gave the tetracyclic system in high yield by a classical cyclization reaction (Scheme 18).

The scope of the approach was explored, and it was found to be suitable for the total synthesis of flavopereirine and isonauclefidine, both of which are advanced intermediates for the synthesis of deplancheine, mitragynine, rutaecarpine, norketoyobyrine, and an analogue of javacarboline in good overall yields.

The synthesis of the 5-amino derivative of naphtho[2,1,8-*ija*]quinolizinium (**22**) was reported by Gryko and co-workers.[45] The procedure is based on an intramolecular process analogue of the Houben−Hoesch reaction involving acid activation of a nitrile (Scheme 19).

We reported four previously unknown AZAHs (**23−26**) by a Westphal-type condensation between the glyoxal equivalent [1,4]dioxane-2,3-diol (DODO) or acenaphthenequinone and the corresponding *N*-aminoazinium or azolium salts[46] obtained by *N*-amination of azines and azoles with *O*-(mesitylenesulfonyl)hydroxylamine (MSH) (Scheme 20).

We also described the first synthesis of symmetrical biquinolizinium cations **27−29**, which was achieved by a palladium-catalyzed coupling reaction from the corresponding bromoquinolizinium bromides[47] (Scheme 21). Theoretical calculations predicted 1,1′- and 4,4′-biquinolizinium dications to be chiral molecules, with the latter having such a high energy of formation that this factor is likely to account for the failure to form this dicationic system.

Arai and Sato reported the formation of some AZAHs (**30−34**) by oxidative photocyclization processes. Aerated solutions of styryl-substituted quinolizinium and benzo[*a*]quinolizinium salts were converted into different polycyclic cations by irradiation in the presence of iodine.[48] A double photocyclization of the 2,8-distyrylquinolizinium salt led to dinaphtho[1,2-*a*:2′,1′-*h*]quinolizinium, bis[1]benzothieno[7,6-*a*:6′,7′-*h*]quinolizinium, and bis[1]benzothieno[4,5-*a*:5′,4′-*h*]-quinolizinium perchlorates (**35−37**)[49] (Scheme 22).

Lainé and Mullen also used oxidative photo-biscyclization reactions of polyaryl-substituted pyridinium salts to obtain several benzo[1,2]quinolizino[3,4,5,6-*def*]phenanthridinium and benzo[*c*]benzo[1,2]quinolizino[3,4,5,6-*ija*][1,6]-naphthyridin-15-ium salts **38** and **39** in moderate yields[50] (Scheme 23).

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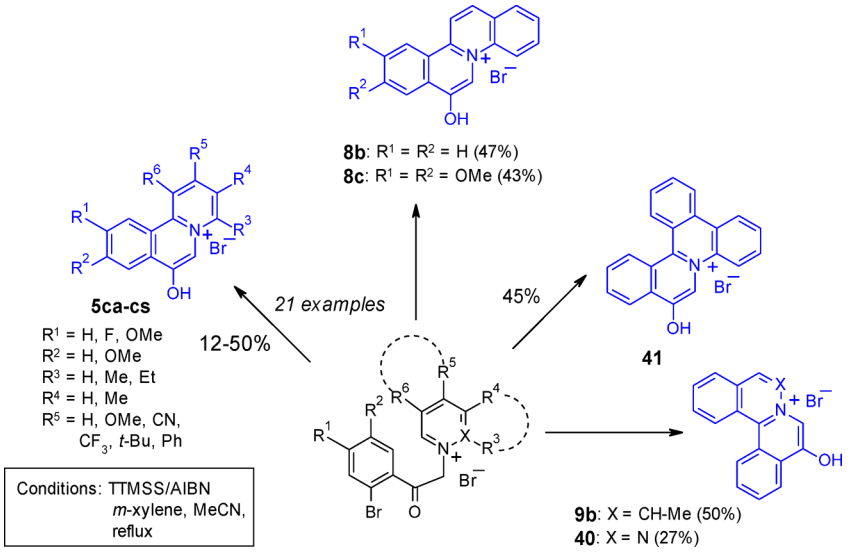
Scheme 24. Synthesis of AZAHs by Intramolecular Radical Arylation



Finally, we reported a synthesis of 7-hydroxybenzo[*a*]-quinolizinium derivatives by intramolecular radical arylation of the appropriate *N*-[2-(2-bromophenyl)-2-oxoethyl]pyridinium salts. Reactions were carried out using 2 equiv of both tris(trimethylsilyl)silane (TTMSS) and AIBN in *m*-xylene under reflux[51] (Scheme 24). The procedure was extended to other polycyclic systems such as dibenzo[*a*,*f*]quinolizinium, dibenzo[*a*,*h*]quinolizinium, isoquino[1,2-*a*]phthalazin-7-ium, and isoquino[2,1-*f*]phenanthridinium salts.

In summary, we have surveyed the recent and novel approaches to AZAHs. The most general and innovative synthetic methodologies are mainly based on RCM reactions and annulation reactions through C−H activation. Both strategies are proving to be very efficient for the synthesis of these charged heterocycles, thus allowing the preparation of new heterocyclic systems and improved syntheses of others obtained by classical methods, which in many cases require harsher conditions and lack generality.

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Notes

The authors declare no competing financial interest.

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David Sucunza received his Ph.D. in organic chemistry from the University of La Rioja, Spain, in 2003. After postdoctoral stays at the Universities of Cologne, Germany, and Manchester, U.K., he is currently associate professor at the University of Alcalá in Madrid, Spain.

Ana M. Cuadro obtained her M.Sc. from Complutense University of Madrid. After a stay in the Institut of Medicinal Chemistry−CSIC, Madrid, she completed her Ph.D. at Alcalá University, spending a postdoctoral stay at the Imperial College of Science & Technology (U.K.). Then she spent short stays in Massachusetts Institute of Technology (MIT) and in the Chemistry Research Laboratory (CRL) in Oxford University. In 1994, she got a lecturership in Organic Chemistry at the University of Alcalá, being since 2001 senior lecturer. Her current research interest focuses on synthesis, reactivity, and NLO properties on heteroaromatic cations.

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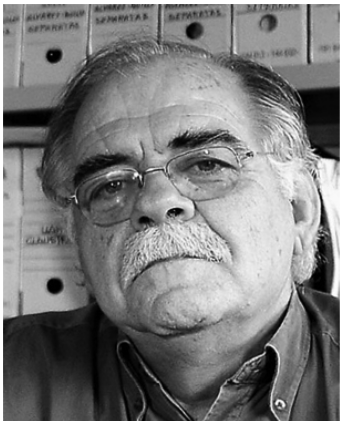

Julio Alvarez-Builla obtained his Ph.D. at the University Complutense of Madrid and spent a postdoctoral stage with Prof. A.R. Katritzky at the University of East Anglia (U.K.). In 1981, he got a lecturership in Organic Chemistry at the University of Alcalá, becoming full professor in 1992. His current research interest focuses on the synthesis of heterocyclic compounds with pharmaceutical interest.

Juan J. Vaquero obtained a Ph.D. from the University of Alcalá, Spain. After a postdoctoral stay at the Imperial College of Science & Technology (U.K.), he joined the University of Alcalá, where he has been full professor of Organic Chemistry since 1998. Major research interests include the chemistry, biology, and applications of heteroaromatic cations, the design and synthesis of bioactive compounds against targets involved in renal disease, and the total synthesis of bioactive alkaloids.

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■ REFERENCES

(1) The term "*azonia*" was used for the first time in 1965 by Bradsher: Bradsher, C. K.; Kimber, R. W. L. *J. Org. Chem.* **1965**, *30*, 1846. Bradsher used the term "*azonialog*" for the heteroaromatic cation resulting from the substitution of a bridgehead carbon by a nitrogen in the corresponding aromatic hydrocarbon. Although aromatic *azinium* and *azolium* salts could also be formally considered as azonia aromatic heterocycles, both terms are of general use and are accepted to refer to salts generated by the quaternization of azines and azoles, respectively.

(2) Some of the parent tetracyclic systems and most of the pentacyclic systems remain unknown.

(3) For recent selected examples, see: (a) Bortolozzi, R.; Ihmels, H.; Thomas, L.; Tian, M.; Viola, G. *Chem. - Eur. J.* **2013**, *19*, 8736. (b) Mayer, U. F. J.; Murphy, E.; Haddow, M. F.; Green, M.; Alder, R. W.; Wass, D. F. *Chem. - Eur. J.* **2013**, *19*, 4287. (c) Cañeque, T.; Cuadro, A. M.; Alvarez-Builla, J.; Perez-Moreno, J.; Clays, K.; Castaño, O.; Andres, J. L.; Vaquero, J. J. *Dyes Pigm.* **2014**, *101*, 116. (d) Bortolozzi, R.; von Gradowski, S.; Ihmels, H.; Schafer, K.; Viola, G. *Chem. Commun.* **2014**, *50*, 8242. (e) Fei, X.; Li, R.; Lin, D.; Gu, Y.; Yu, L. *J. Fluoresc.* **2015**, *25*, 1251. (f) Yue, X.; Armijo, Z.; King, K.; Bondar, M. V.; Morales, A. R.; Frazer, A.; Mikhailov, I. A.; Przhonska, O. V.; Belfield, K. D. *ACS Appl. Mater. Interfaces* **2015**, *7*, 2833. (g) Marcelo, G.; Pinto, S.; Cañeque, T.; Mariz, I. F. A.; Cuadro, A. M.; Vaquero, J. J.; Martinho, J. M. G.; Maçoas, E. M. S. *J. Phys. Chem. A* **2015**, *119*, 2351.

(4) For the first synthesis of parent quinolizinium, see: (a) Boekelheide, V.; Gall, W. G. *J. Am. Chem. Soc.* **1954**, *76*, 1832. For other syntheses, see: (b) Boekelheide, V.; Ross, J. M. *J. Am. Chem. Soc.* **1955**, *77*, 5691. (c) Miyadera, T.; Iwai, I. *Chem. Pharm. Bull.* **1964**, *12*, 1338.

(5) Thyagarajan, B. S. *Adv. Heterocycl. Chem.* **1965**, *5*, 291.

(6) Jones, G. *Adv. Heterocycl. Chem.* **1982**, *31*, 1.

(7) (a) Ihmels, H. *Science of Synthesis*; Georg Thieme: Stuttgart, 2005; Vol. *15*, p 907. (b) Ihmels, H. *Science of Synthesis, Knowledge Updates*; Georg Thieme: Stuttgart, 2011; Vol. *1*, p 75.

(8) Vaquero, J. J.; Alvarez-Builla, J. Heterocycles Containing a Ring-Junction Nitrogen. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011; Vol. *4*, Chapter 22, pp 1989−2070.

(9) Arai, S.; Hida, M. *Adv. Heterocycl. Chem.* **1992**, *55*, 261.

(10) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.

(11) For leading references, see: (a) Schmidt, B.; Hauke, S.; Krehl, S.; Kunz, O. Ring-Closing Metathesis. In *Comprehensive Organic Synthesis*, 2nd ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: Amsterdam, 2014; Vol. *5*, pp 1400−1480. (b) Mulzer, J.; Ohler, E.; Gaich, T. Ring-Closing Olefin Metathesis for Organic Synthesis. In *Comprehensive Organometallic Chemistry III*; Mingos, D., Michael, P., Crabtree, R. H., Eds.; Elsevier: Amsterdam, 2007; Vol. *11*, pp 207−269. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

(12) The quinolizinium system can obtained in a ring-closing metathesis process which would involve the formation of α, β, and γ bonds with respect to the nitrogen atom of the azinium substrate. In practice, however, the approach to quinolizinium from the dipropenyl azadiene was unsuccessful because this diene could not be obtained under any of the conditions tested.

(13) Nuñez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2004**, *6*, 4125.

(14) The best synthesis of the quinolizinium bromide was also reported in 54% overall yield. See reference 4c.

(15) Núñez, A.; Abarca, B.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem.* **2009**, *74*, 4166.

(16) For previous syntheses of the parent heterocycle, see: (a) Pollak, A.; Stanovnik, B.; Tišler, M. *J. Org. Chem.* **1971**, *36*, 245. (b) Sawyer, J. R. H.; Wibberley, D. G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1138−1143. (c) Fischer, G. W. *J. Prakt. Chem.* **1974**, *316*, 474. (d) Tamura, S.; Ono, M. *Chem. Pharm. Bull.* **1978**, *26*, 3167.

(17) Abengozar, A.; Abarca, B.; Cuadro, A. M.; Sucunza, B.; Alvarez-Builla, J.; Vaquero, J. *J. Eur. J. Org.* **2015**, *2015*, 4214.

(18) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55−66.

(19) Nuñez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Chem. Commun.* **2006**, 2690.

(20) Glover, E. E.; Jones, G. *J. Chem. Soc.* **1958**, 3021.

(21) Kimber, R. W. L.; Parham, J. C. *J. Org. Chem.* **1963**, *28*, 3205.

(22) Arai, S.; Takeuchi, T.; Ishikawa, M.; Takeuchi, T.; Yamazaki, M.; Hida, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, *3*, 481.

(23) Nuñez, A.; Abarca, B.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Eur. J. Org. Chem.* **2011**, *2011*, 1280.

(24) Nuñez, A.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2007**, *9*, 2977.

(25) Bradsher, C. K.; Beavers, L. E. *J. Am. Chem. Soc.* **1955**, *77*, 453.

DOI: 10.1021/acs.joc.6b01092
J. Org. Chem. 2016, 81, 10126−10135

(26) (a) Bradsher, C. K.; Solomons, T. W. G.; Vaughan, F. R. *J. Org. Chem.* **1960**, *25*, 757. (b) Bradsher, C. K.; Parham, J. C. *J. Org. Chem.* **1963**, *28*, 83.
(27) Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1980**, *45*, 4248.
(28) Abarca, B.; Custodio, R.; Cuadro, A. M.; Sucunza, D.; Domingo, A.; Mendicuti, F.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2014**, *16*, 3464.
(29) For previous syntheses, see: (a) Gribble, G. W.; Johnson, D. A. *Tetrahedron Lett.* **1987**, *28*, 5259. (b) Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773. (c) Fürstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7329. (d) Kraus, G. A.; Malpert, J. H. *Synlett* **1997**, *1997*, 107. (e) Lipinska, T. *Tetrahedron* **2006**, *62*, 5736.
(30) Luo, C.-Z.; Gandeepan, P.; Cheng, C.-H. *Chem. Commun.* **2013**, *49*, 8528.
(31) Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 8850.
(32) Davies, D. L.; Ellul, C. E.; Macgregor, S. A.; McMullin, C. L.; Singh, K. *J. Am. Chem. Soc.* **2015**, *137*, 9659.
(33) (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13.
(34) Luo, C.-Z.; Gandeepan, P.; Wu, Y.-C.; Tsai, C.-H.; Cheng, C.-H. *ACS Catal.* **2015**, *5*, 4837.
(35) Two syntheses have previously been reported for the parent benzo[*c*]quinolizinium by two cyclization methods involving the formation of C1−N11 and C10a−N11 bonds. See: (a) Glover, E. E.; Jones, G. *J. Chem. Soc.* **1958**, 3021. (b) Fozard, A.; Bradsher, C. K. *J. Org. Chem.* **1966**, *31*, 2346.
(36) (a) Wang, Z.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 4790. (b) Zhang, J.; Chen, H.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2768. (c) Li, J.; John, M.; Ackermann, L. *Chem. - Eur. J.* **2014**, *20*, 5403.
(37) Prakash, S.; Muralirajan, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1844.
(38) Ghorai, D.; Choudhury, J. *Chem. Commun.* **2014**, *50*, 15159.
(39) Ghorai, D.; Choudhury, J. *ACS Catal.* **2015**, *5*, 2692.
(40) (a) Thenarukandiyil, R.; Choudhury, J. *Organometallics* **2015**, *34*, 1890. (b) Ghorai, D.; Dutta, C.; Choudhury, J. *ACS Catal.* **2016**, *6*, 709.
(41) Ge, Q.; Li, B.; Song, H.; Wang, B. *Org. Biomol. Chem.* **2015**, *13*, 7695.
(42) Li, R.; Hu, Y.; Liu, R.; Hu, R.; Li, B.; Wang, B. *Adv. Synth. Catal.* **2015**, *357*, 3885.
(43) Ge, Q.; Hu, Y.; Li, B.; Wang, B. *Org. Lett.* **2016**, *18*, 2483.
(44) Pan, X.; Bannister, T. D. *Org. Lett.* **2014**, *16*, 6124.
(45) Stasyuk, A. J.; Smolen, S.; Glodkowska-Mrowka, E.; Brutkowski, W.; Cyranski, M. K.; Tkachenko, N.; Gryko, D. T. *Chem. - Asian J.* **2015**, *10*, 553.
(46) Suárez, R. M.; Bosch, P.; Sucunza, D.; Cuadro, A. M.; Domingo, A.; Mendicuti, F.; Vaquero, J. J. *Org. Biomol. Chem.* **2015**, *13*, 527.
(47) García-Cuadrado, D.; Cuadro, A. M.; Alvarez-Builla, J.; Sancho, U.; Castaño, O.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 5955.
(48) (a) Sato, K.; Katayama, Y.; Yamagishi, T.; Arai, S. *J. Heterocycl. Chem.* **2006**, *43*, 177. (b) Arai, S.; Yoda, H.; Sato, K.; Yamagishi, T. *J. Heterocycl. Chem.* **2002**, *39*, 425.
(49) Sato, K.; Okazaki, S.; Yamagishi, T.; Arai, S. *J. Heterocycl. Chem.* **2004**, *41*, 443.
(50) (a) Wu, D.; Zhi, L.; Bodwell, G. J.; Cui, G.; Tsao, N.; Müllen, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5417. (b) Fortage, J.; Tuyéras, F.; Ochsenbein, P.; Puntoriero, F.; Nastasi, F.; Campagna, S.; Griveau, S.; Bedioui, F.; Ciofini, I.; Lainé, P. P. *Chem. - Eur. J.* **2010**, *16*, 11047. (c) Fortage, J.; Peltier, C.; Nastasi, F.; Puntoriero, F.; Tuyéras, F.; Griveau, S.; Bedioui, F.; Adamo, C.; Ciofini, I.; Campagna, S.; Lainé, P. P. *J. Am. Chem. Soc.* **2010**, *132*, 16700.
(51) Castillo, R.; Burgos, C.; Vaquero, J. J.; Alvarez-Builla, J. *Eur. J. Org. Chem.* **2011**, *2011*, 619.

DOI: 10.1021/acs.joc.6b01092
J. Org. Chem. 2016, 81, 10126−10135