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PII: S0040-4039(15)30079-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.09.035
Reference: TETL 46707

To appear in: *Tetrahedron Letters*

Received Date: 18 August 2015
Revised Date: 9 September 2015
Accepted Date: 13 September 2015

Please cite this article as: Yaragorla, S., Singh, G., Dada, R., $C_{(sp3)}$–H functionalization of methyl azaarenes: A Calcium-catalyzed facile synthesis of (*E*)-2-Styryl azaarenes and 2-aryl-1,3-bisazaarenes, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.09.035

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Tetrahedron Letters
journal homepage: www.elsevier.com

$C_{(sp3)}$–H functionalization of methyl azaarenes: A Calcium-catalyzed facile synthesis of (*E*)-2-Styryl azaarenes and 2-aryl-1,3-bisazaarenes

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
SP^3 C-H Functionalization
Styryl azaarenes
Ca(II) catalysis
Multicomponent reactions
Solvent free synthesis
Heterocyclic compounds

ABSTRACT

Alkaline earth (Ca^{2+}) catalysed sp^3 C-H functionalization of methyl azaarenes for the synthesis of biologically important (*E*)-2-styryl azaarenes, 2-aryl-1,3-bisazaarenes and 3,3-bisazaarenyl indolinones has been described. Initially methyl azaarens react with aryl aldehydes to give β-hydroxy derivatives, which undergo Ca(II) catalysed thermodynamic elimination to give the styryl azaarenes in a single step. Similarly it may undergo S_N1 reaction to give 2-aryl-1,3-bisazaarenes and 3,3-bisazaarenyl indolinones (if isatin used as the electrophile). This green synthetic methodology enjoys the simple reaction procedures, solvent free conditions, step economy, substrate diversity and high yields of the products in short time.

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Methyl azaarenes are important class of feed stock materials for the synthesis of variety of biologically active *N*-heterocyclic compounds.[1] Owing to the biological importance and structural features of methyl azaarenes, several derivatives have been synthesized (Figure 1) by the functionalization of sp3 C-H bond.[2-7, 12-17.] In all the cases methyl azaarenes behave as a nucleophile and adds to the variety of activated electrophiles to produce the corresponding azaarene derivatives. For example, as shown in the Figure 1, they react with aldehydes to produce β-hydroxy azaarenes (**I**),[2] styryl azaarenes (**VI**) and β-aryl 1,3-bisazaarenes (**V**).[3] Similarly they react with imines to produce β -amino azaarenes (**II**)[4] and styryl azaarenes,[5] with isatin they delivered 3-hydroxy azaarenyl indolinones (**IV**)[6] and with ethyl glyoxalates they furnished β-hydroxy esters of azaarenes (**III**)[6] etc.[7] Due to these intriguing features C-H functionalization of methylazaarenes has been attracted many of the synthetic groups over the globe to develop the suitable catalytic conditions for the synthesis of variety of azaarene deivatives.

Styryl azaarenes are important bioactive compounds[8] and key building blocks for the synthesis of 2-alkyl heterocyclic compounds[9] (Figure 1). For example FZ41, KHD161 act as a promising HIV integrase inhibitor through a previously unknown mechanism.[10] Montelukast sodium (by Merck) is used as potent anti-asthma drug.[11] Previously styryl azaarenes had been synthesized from the suitable reactants by the use of transition metal catalysts,[12] refluxing in toluene with p-toluenesulfonamide,[5,13] a two-step synthesis using CAN,[14a] n-BuLi/MsCl[14b] and Ac_2O/pyridine;[15] and through Wittig reaction.[16] Musiol *et al.*[17] reported the catalyst free synthesis under mw irradiation but only limited to the activated quinaldines that too with very low yields.[17c] Albeit some elegant methods have been emerged for the synthesis of styryl azaarenes, most of them were reported with toxic solvents (toluene) stoichiometric amounts of reagents (Ac_2O, Pyridine), expensive transition metals as the catalysts, longer reaction times, poor yields and sometimes two-step procedures.

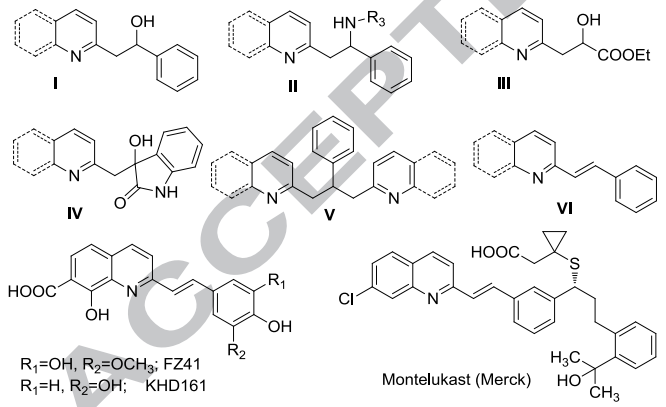
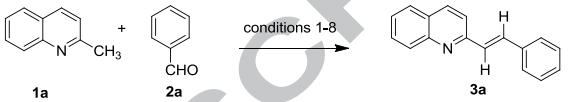


Figure 1. Representative structures of azaarene derivatives.

2-aryl-1,3-bis azaarenes are new class of azaarene derivatives, which could be synthesized by the sp3 C-H activation of methyl azaarenes. Recently Guo *et al.* has reported the synthesis of these dimeric compounds by refluxing quinaldine and aldehyde in xylene at 120 °C in presence of 10 mol% of TsOH.[3] Owing to the above mentioned limitations, it is highly desirable to develop a mild, high efficient and sustainable catalytic system for the step economy synthesis of styryl azaarenes and bisazaarenes.

In the recent years alkaline earth (**ae**) metal catalysts have been proved as an alternative to the many of the transition metal catalysts which are less abundant and highly expensive.[18] Among them Ca(II) became more attarctive green-Lewis acid catalyst due to its high abundance, less expensive and stability towards moisture and water.[19] Recently we have showed the utility of $Ca(OTf)_2$ as a green catalyst in the Ritter reaction,[21a] in the cascade synthesis of pyranocoumarins[21b] and benzo[b]pyrans and in the multi component synthesis of benzylpyrazolyl coumarins.[21c] In continuation of our research aimed towards the development of sustainable synthetic methodologies for the synthesis of biologically interesting small molecules,[21] herein we report a facile approach for the synthesis of (*E*)-2-styryl azaarenes and 2-aryl-1,3-bisazaarenes *via* $Ca(OTf)_2$ catalysed sp^3 C-H functionalization of azaarenes.

Table 1. Optimization studies for the synthesis of styryl azaarene **3a** from quinaldine **1a** and benzaldehyde **2a**.



Entry	$Ca(OTf)_2$ (mol%)	Bu_4NPF_6 (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	5	5	H_2O	100	24	40
2	5	5	toluene	120	5	70
3	5	5	neat	120	5	80
4	5	5	neat	130	5	96
5	5	0	neat	130	8	94
6[b]	5	2	neat	130	5	96
7	0	5	neat	130	24	40
8	0	0	neat	130	24	35

[a] Isolated yields. [b] Optimum conditions

Initially, we started the synthesis of styryl azaarenes by refluxing the stoichiometric amounts of 2-methyl quinoline (**1a**) and benzaldehyde (**2a**) in presence of $Ca(OTf)_2$ (5 mol%) and Bu_4NPF_6 (5 mol%) in water at 100 °C (entry 1, Table 1). After continuing the reflux for 24 h we isolated the desired (*E*)-2-styrylquinoline **3a** in 40% yield along with 55% of 1-phenyl-2-(quinolin-2-yl)ethanol (**III,** Scheme 3). Though the starting materials were completely consumed we could isolate only 40% of the product because the major portion of the alcohol did not undergo eliminaion. Due to this reason we tried the next reaction high temperature (120 °C) in toluene and isolated 70% of the product **3a** after 5 h (entry 2, Table 1). Encouraged by this result, we further conducted several experiments for the optimization of the reaction conditions (Table 1). When the reaction was run under solvent-free conditions at 130 °C product **3a** was isolated in 96% yield (entry 4, Table 1). To check the role of additive, we repeated the reaction in the absence of Bu_4NPF_6 (entry 5, Table 1) and noticed that the reaction is equally working (94%) but taking 8 h to complete. This indicates that the reaction is working well with the catalyst alone (5 mol%) but when additive is added the reaction time is falling from 8 h to 5 h. Another reaction was performed to minimize the loading of additive and found that with 2 mol% of additive along with 5 mol% Ca(II) at 130 °C the product **3a** was isolated in 96% after 5 h (entry 6, Table 1). With obvious perceptible decrease in the reaction time (from 8 h to 5 h), use of additive (2 mol%) has been considered as the better condition (entry 6, Table 1) for making the variety of styryl azaarenes. After having the optimum conditions in hand, our immediate goal was to check the scope and generality of Ca(II)-catalyzed solvent-free synthesis of styryl azaarenes *via* C-H functionalization of azaarenes (entry 6, Table 1). As shown in the Table 2, a range of aldehydes (entries 1-9, 24) were reacted with the variety of azaarenes such as 2-methylquinoline (**1a**), 7-chloro-2-methylquinoline (**1d**), 2-methylpyridine (**1b**) and lutidine (**1c**). Tolualdehyde (**2b,** alkyl substitution, +I), 4-nitrobenzaldehyde (**2c,** electron withdrawing group, -I), halogenated aldehydes (**2d**, **2e**, **2f**) were competently reacted

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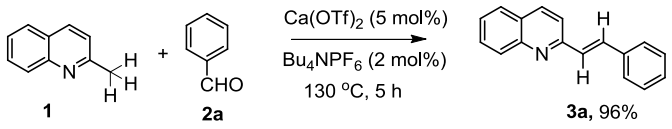
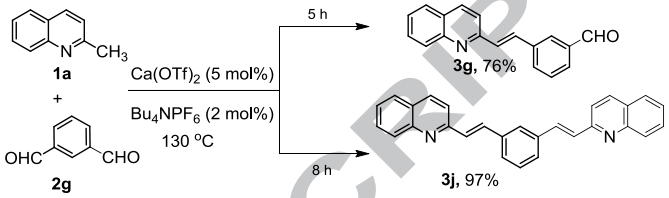
with quinaldine (**1a)** within 4-5 h to yield corresponding styryl azaarenes in good to excellent yields (entries 2-6, Table 2). Sterically rich aldehyde like vaniline (**2i**) also gave 89% yield with quinaldine (**1a**). Heterocyclic aldehyde 2-furaldhyde (**2h**) gave excellent yield 96% with **1a** within 5 h (Table 2, entry 8). Selective mono-styrylation of benzene-1,3-dialdehyde (**2g)** has been achieved in 76% by using one equivalent quinaldine **1a** (entry 7, Table 2). When the double stoichiometric amounts of **1a** were used against **2g**, styryl bisazaarene **3j** was isolated in 97% after 8 h (Scheme 2).



Scheme 1. Optimum reaction conditions for the C-H functionalization of quinaldine with benzaldehyde

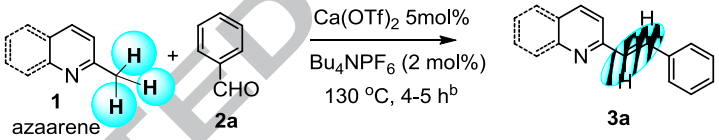
After checking the efficacious participation of range of aldehydes against quinaldine **1a** in the methodology we extended our focus to check the scope of different 2-methyl azaarenes. Hence 2-methylpyridine (**1b**) was used against benzaldehyde, 4-nitrobenzaldehyde and we were glad to isolate the desired products **3k**, **3l** in 86, 98% respective yields after 8 h. 7-chloroquinaldine (**1d**) also reacted with the range of benzaldehydes, furaldehyde and pyridine 3-carboxaldehyde (**2j**) to furnish the respective styryl azaarenes (entries 19-28) in good to excellent yields. Entry 28 (Table 2) describes an interesting example, the product **3ab** obtained here is an intermediate compound in the synthesis of antiasthma drug montelukast[11b] by Merck company (Figure 1). Another interesting methyl azaarene, lutidine (**1c**) which is having two methyl groups on 2, 5 positions on pyridine has been also studied. Lutidine was selectively styrylated with benzaldehyde **2a** and 4-nitrobenzaldehyde **2c** to yield (*E*)-2-methyl-6-styrylpyridine (**3m**) and (*E*)-2-methyl-6-(4-nitrostyryl)pyridine **3n** in 62, 89% respectively after 8 h. When two moles of aryl aldehydes were used then both methyl groups of lutidine were functionalized to the corresponding bisstyrylazaarenes in good to excellent yields after 12 h (entries 15-18, Table 2).

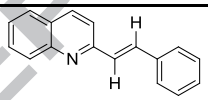
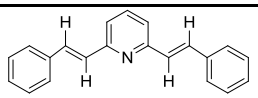
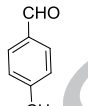
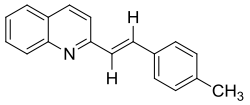
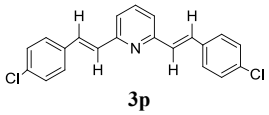
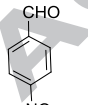
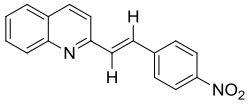
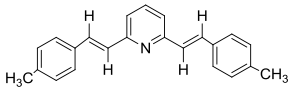
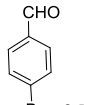
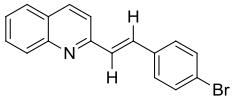
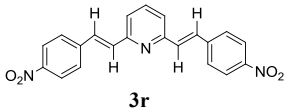
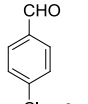
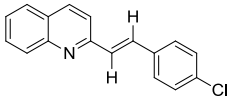
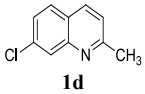
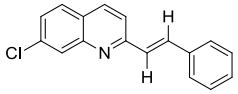
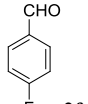
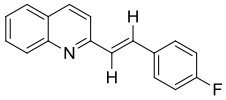
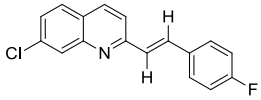


Scheme 2. Reaction of quinaldine with benzene-1,3-dialdehyde

A plausible mechanism for this transformation has been described in the Scheme 3. Initially quinaldine forms the complex **I** with $Ca(OTf)_2$, which will undergo nucleophilic addition on the activated benzaldehyde (by Ca^{2+}) **II** to give the intermediate **III**. In the next step intermediate **III** may undergo E_2-elimination (**IV**) to give the desired styryl azaarene **3a**. Alternatively intermediate **III** may result in the formation of carbocation **V** which may again undergo E_1 elimination to give **3a.**

Table 2. Substrate scope in the Ca(II)-catalyzed sp^3 C-H activation of methyl azaarenes for the facile synthesis of styryl azaarenes.[a]



Entry	Aldehyde	Azaarene	Styryl azaarene	Yield(%)[c]	Entry	Aldehyde	Azaarene	Styryl azaarene	Yield (%)[c]
1	 **2a**	 **1a**	 **3a**	96	15	**2a**	**1c**	 **3o**	73
2	 **2b**	**1a**	 **3b**	81	16	**2e**	**1c**	 **3p**	91
3	 **2c**	**1a**	 **3c**	98	17	**2b**	**1c**	 **3q**	72
4	 **2d**	**1a**	 **3d**	94	18	**2c**	**1c**	 **3r**	63
5	 **2e**	**1a**	 **3e**	97	19	**2a**	 **1d**	 **3s**	96
6	 **2f**	**1a**	 **3f**	88	20	**2f**	**1d**	 **3t**	81

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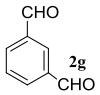
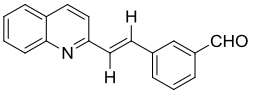
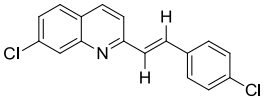
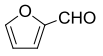
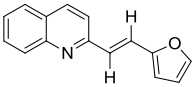
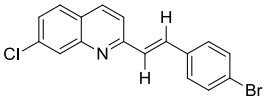
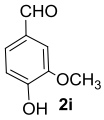
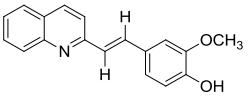
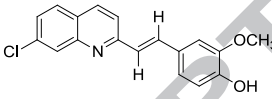
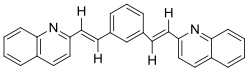
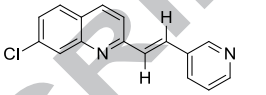
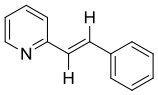
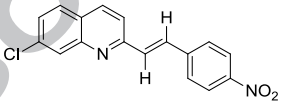
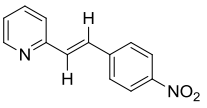
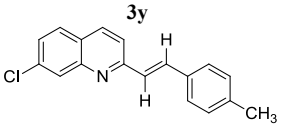
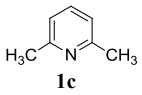
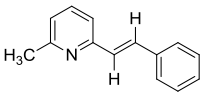
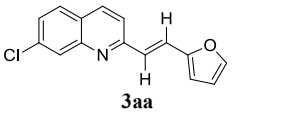
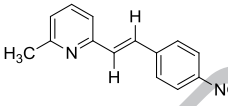
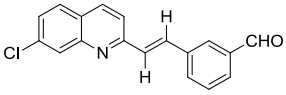
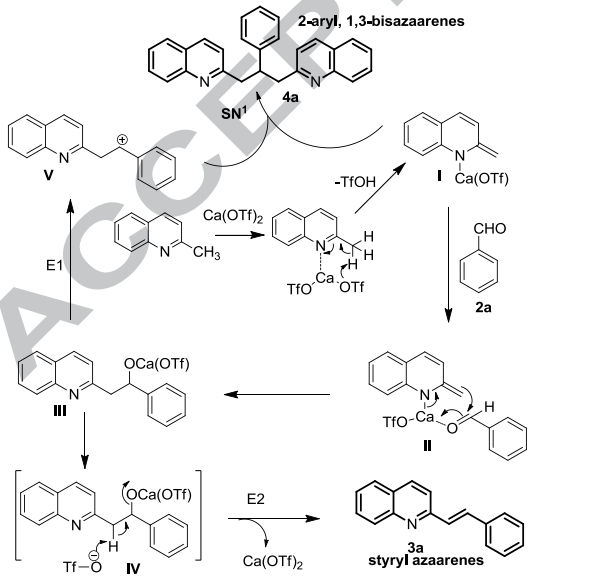
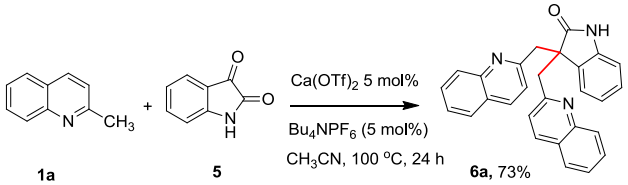
7	 **2g**	**1a**	 **3g**	76	21	**2e**	**1d**	 **3u**	93
8	 **2h**	**1a**	 **3h**	96	22	**2d**	**1d**	 **3v**	72
9	 **2i**	**1a**	 **3i**	89	23	**2i**	**1d**	 **3w**	69
10	**2g**	**1a**	 **3j**	97	24	 **2j**	**1d**	 **3x**	95
11	**2a**	 **1b**	 **3k**	86	25	**2c**	**1d**	 **3y**	94
12	**2c**	**1b**	 **3l**	98	26	**2b**	**1d**	 **3z**	92
13	**2a**	 **1c**	 **3m**	62	27	**2h**	**1d**	 **3aa**	66
14	**2c**	**1c**	 **3n**	89	28	**2g**	**1d**	 **3ab**	93

[a] Reaction conditions: stoichiometric amounts of reactants, 5 mol% of $Ca(OTf)_2$ and 2 mol% Bu_4NPF_6 were heated in closed vessel at 130 °C for 4-5 h. [b] In case of 2-methyl pyridine and 2,6-lutidine reaction completes in 7-10 h; [c] Isolated yields after column chromatography.



Scheme 3. Plausible mechanism for the Ca(II) catalysed C-H functionalization of azaarenes.

It is envisioned that if there is a carbocation formation (solution phase) it may undergo nucleophilic substitution (S_N1) with another mole of activated quinaldine to produce the bisazaarene **4a**. A reaction was performed to find out the possibility of carbocation formation, in which a styryl azaarene (**3c**) and quinaldine (**1a**) were treated under similar conditions and found only 15-20% of the dimeric compound **4a**. This illustrates that the dimer may be the result of S_N1 type reaction. Based on this hypothesis we commenced the synthesis of 2-aryl, 1,3-bisazaarenes by taking two moles of quinaldine **1a** and one mole of 4-nitrobenzaldehyde (**2c**) in presence of $Ca(OTf)_2$ (5 mol%) and Bu_4NPF_6 (5 mol%). It is evidenced from the table 1 that at high temperature and neat conditions reaction is favoring the elimination to form the styryl azaarenes. Hence we decided to run the reaction in water at 100 °C and isolated 25% of required dimer **4a**, 35% eliminated product **3a** and 30% alcohol (**III**). After performing several experiments we found that the reaction is giving best results at 100 °C in acetonitrile (86% of **4a** along with 8% **3a**). Subsequently having the suitable conditions in hand, tolualdehyde (**2b**), 4-bromobenzaldehyde (**2d**), 4-chlorobenzaldehyde (**2e**) and 4-fluorobenzaldehyde (**2f**) were treated under same conditions with quinaldine and isolated the respective bisazaarenes (**4b-4e**) in good yields as showed in Table 3. Similarly 7-chloroquinaldine (**1d**) was also reacted with 4-bromo, 4-chloro, 4-fluoro and 4-nitrobenzaldehydes under the same reaction conditions to furnish the respective bisazaarenes (**4f, 4g, 4h** and **4i**) in good yields (Table 3).



Scheme 4. Calcium catalysed synthesis of 3,3-bis(quinolin-2-ylmethyl)indolin-2-one

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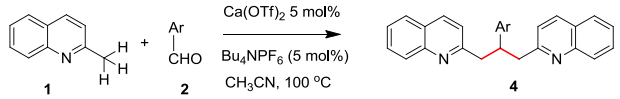
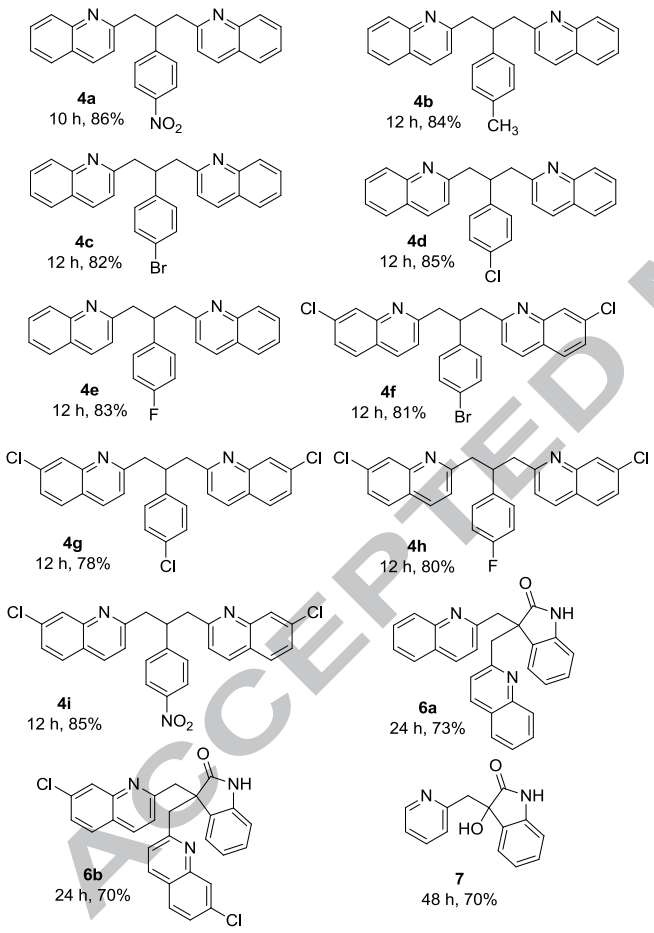
To check the scope of this methodology isatin (**5**) was used as the electrophile and treated with quinaldine to isolate 3,3-bis(quinolin-2-ylmethyl)indolin-2-one (**6a**) in 73% yield after 24 h (Scheme 4). Similarly quinaldine **2d** also reacted with isatin to furnish 70% of **6b** after 24 h. When 2-methylpyridine **1b** was used as the nucleophile against isatin we could not see the expected product even after 48 h but the formation of intermediate alcohol 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-one (**7**) was observed (entry 8, Table 3).

Table 3. sp^3 C-H functionalization of methylazaarenes with various electrophiles for the synthesis of bisazaarenes.[a]





[a] quinaldine (2 equiv) and aldehyde (1 equiv) were refluxed in CH_3CN in presence of 5 mol% of $Ca(OTf)_2$ and 5 mol% of Bu_4NPF_6 at 100 °C till the completion of the reaction. [b] isolated yields after column chromatography

In summary, we have developed a mild, efficient and sustainable catalytic system for the sp^3 C-H functionalization of methyl azaarenes. Biologically important (*E*)-2-styryl azaarenes, 3,3-bismethyl azaarenyl indolinones and 2-aryl-1,3-bisazaarenes have been synthesized in excellent yields using simpler reaction conditions. Use of environmentally benign and inexpensive catalyst, step economy, solvent-free conditions (for styryl azaarenes), high yields and substrate diversity are some of the key features of our methodology, which gives the simple and rapid access to the titled compounds which are of great interest in the medicinal and pharmaceutical chemistry.

Acknowledgments

SY acknowledge DST-India, for their financial support. GS and RD thank Central University of Rajasthan and CSIR for their fellowships respectively.

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21. General experimental procedure and copies of spectra were provided in the supporting information. Spectral data of representative compounds: **(3d)*:*** Pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 8 Hz, 1H), 7.65-7.61 (m, 2H), 7.54-7.49 (m, 5H), 7.38 (d, *J* = 16 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 148.2, 136.4, 135.4, 133.0, 131.9, 129.8, 129.6, 129.2, 128.6, 127.5, 127.4, 126.3, 122.5, 119.3; IR (KBr) υ: 3047, 2928, 1619, 1592, 1505, 1429, 1402 cm^{-1}. **(6a) :** Red solid. ^{1}H (500 MHz, $CDCl_3$) δ 7.88 (m, 5H), 7.67 (d, *J* = 8 Hz, 2H), 7.56 (t, *J* = 14.9 Hz, 2H), 7.41 (t, *J* = 14.9 Hz, 2H), 7.08 (q, *J* = 6.5, 10, 2H), 7.11-7.06 (m, 2H), 3.76 (d, *J* = 13.7 Hz, 2H, diastereotropic), 3.69 (d, *J* = 13.8 Hz, 2H, diastereotropic) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 181, 157, 147.4, 140.6, 135.7, 129.2, 128.8, 127.7, 127.3, 126.7, 126, 124.9, 122.4, 121.7, 114, 110.1, 109.1, 53.7, 45.5. HRMS (ESI) *m/z* calcd. for $C_{28}H_{21}N_3O$ $[M+H]^+$ 416.1757; found 416.1792. IR (KBr) υ: 3127, 2928, 2350, 1708, 1603, 1474, 1398, 1258 cm^{-1}.

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Graphical Abstract

$C_{(sp3)}$–H functionalization of methyl azaarenes: A Calcium-catalyzed facile synthesis of (*E*)-2-Styryl azaarenes and 2-aryl-1,3-bisazaarenes

Srinivasarao Yaragorla,* Garima Singh and Ravikrishna Dada

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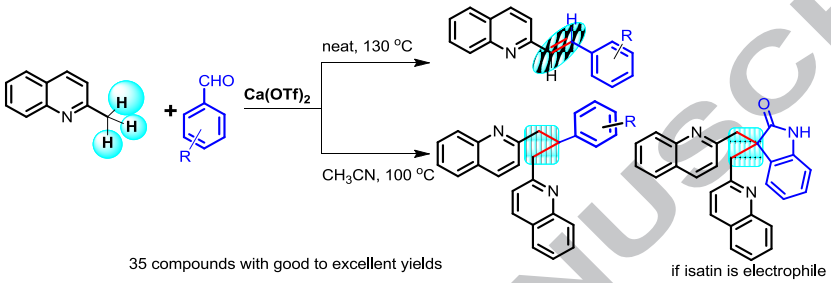

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