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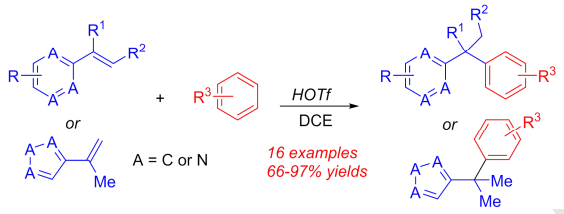

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ABSTRACT

A robust approach to *gem*-dialkylbenzyl heterocycles has been developed through a triflic acid-catalyzed hydroarylation of olefinic heterocycles. A broad range of substrates containing pyridine, quinoline, pyrazole, triazole and imidazole moieties are shown to be highly compatible with this method. This rapid construction of *gem*-dialkyl groups should be useful in the synthesis of drug-like molecules containing heterocyclic diversity and in the study of the *gem*-dialkyl effect.

1. Introduction

Heterocycles, such as pyridine, pyrazole, imidazole and other nitrogen-rich arenes are important pharmacophores, present in numerous approved drugs and drug candidates.[1] As a result, the functionalization of heterocycles has attracted tremendous attention and numerous methods have been developed that allow rapid access to a diverse scope of functionalized heterocycles.[2] Introduction of cyclopropyl or *gem*-dialkyl groups to the benzylic position of heterocycles is of considerable interest in medicinal chemistry and has been shown for instance, to improve the physicochemical and pharmacokinetic properties of drug-like molecules (Figure 1).[3] Specifically, These groups can be incorporated to block the sites of metabolism on benzylic methylenes that are often considered metabolic liabilities. These substituents can also enforce unique conformational biases which can lead to improved binding and increased potency, qualities often sought in medicinal chemistry. In addition, *gem*-dialkyl substituents have been shown to accelerate certain intramolecular cyclization reactions through the Thorpe-Ingold effect. Substrates containing this moiety are therefore of interest in the study and development of synthetic methodologies.[4]

Gem-dialkyl substituents are typically found adjacent to carbonyl groups and often are installed through α-alkylation reactions.[4] In contrast, the introduction of *gem*-dialkyl groups at the benzylic position of arenes, in particular hetero-arenes, remains a challenge and merits further investigation. The hydroarylation reaction of olefinic benzenes under Lewis/Brønsted acidic or transition-metal catalysis is a potential approach to this challenge. Although this strategy has been used

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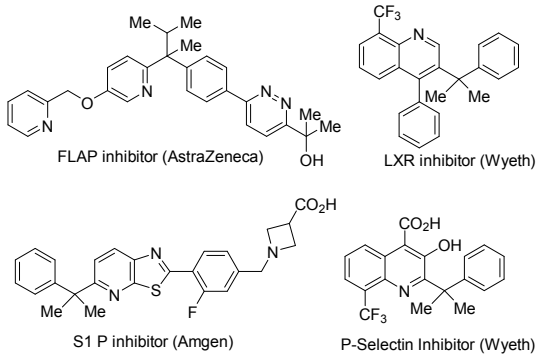
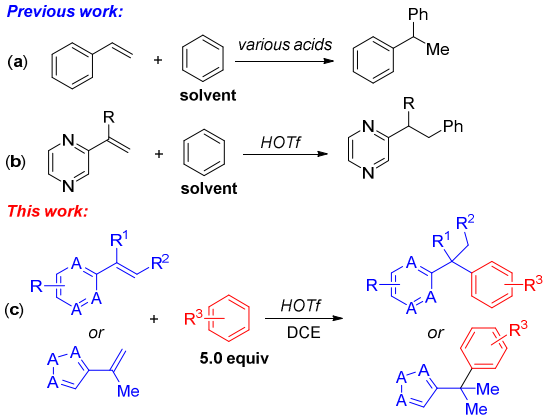


Figure 1. Selected examples of *gem*-dialkylbenzylic heterocycles found in biologically active compounds.

in the synthesis of mono-substituted benzylic arenes (Scheme 1a), it has seldom been applied towards *geminal*-substitution. Moreover, all reported examples of such hydroarylations are performed on simple styrenes which are devoid of heterocyclic diversity.[5] Another approach to *gem*-dialkylbenzylic arenes is base-mediated direct alkylation. For example, the *gem*-dimethyl containing S1 P inhibitor (Figure 1)[3b] was synthesized via a double alkylation reaction[3b] with iodomethane under harsh base conditions. This strategy was presumably facilitated by the enhanced acidity of the benzylic position adjacent to pyridine. Recently, Klumpp and co-workers developed a hydroarylation reaction of olefinic pyrazines and quinoxalines to generate *anti*-Markovnikov addition products using benzene and triflic acid as a co-solvent (Scheme 1b).[6] To our knowledge, no general method exists for the direct synthesis of *gem*-dialkylbenzyl heterocycles

using olefinic hydroarylation. In our efforts to improve the potency and physicochemical properties of a lead series in one of our drug discovery projects, we required a robust method for the introduction of *gem*-dialkylbenzyl heterocycles. Herein, we report an effective triflic acid-catalyzed hydroarylation reaction of olefinic heterocycles for the synthesis of *gem*-dialkylbenzyl heterocycles.

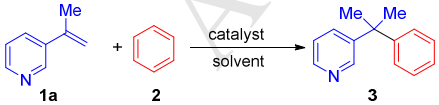


Scheme 1. Examples of Olefin Hydroarylation

2. Results and discussion

As a model substrate, we chose 3-(prop-1-en-2-yl)pyridine **1a** and examined direct hydroarylation with benzene **2**. Various conditions were evaluated and summarized in Table 1. Initial attempts using either Lewis acids or a mild Brønsted acid with benzene as the solvent all failed to provide any expected product (entries 1-3). Of interests, the use of 1.0 equiv of triflic acid afforded the product **3** in 20% yield (entry 4). Increasing the acid loading to 5 equiv dramatically improved the yield to 96% (entry 5). To enhance the utility of this reaction and allow the economical addition of more valuable arenes, we decided to explore reaction conditions that avoided the use of benzene as the solvent. Conducting the reaction with 5 equiv of benzene in DCE as the solvent afforded **3** in 78% yield (entry 6), with some unreacted pyridine **1a**. Increasing the temperature slightly to 100 ^{o}C led to complete consumption of starting material and enhanced the yield to 94% (entry 7). Further decreasing the benzene loading to 2.0 equiv and even 1.0 equiv still provided the product, albeit with lower yields (entries 8 and 9). Using nitromethane, a solvent which is commonly employed in Friedel-Crafts-type reactions, decreased the yield to less than 10%. Conducting the reaction in DCE at 100 ^{o}C with 5 equiv of triflic acid and arenes proved to be the optimal condition.

Table 1. Reaction Optimization



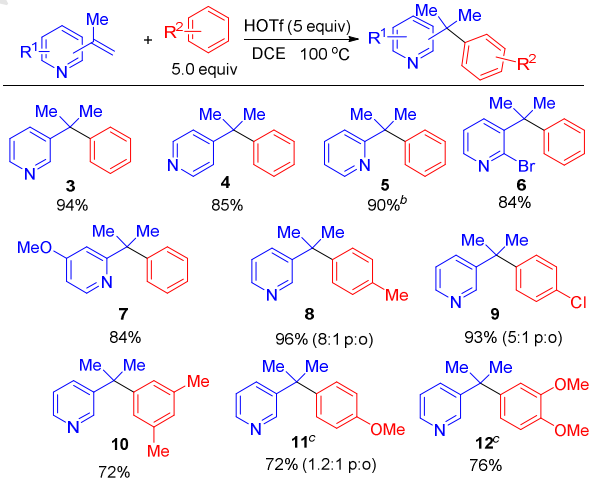
1a 2 3

entry[a]	catalyst	catalyst loading (equiv)	solvent	benzene (equiv)	temp (^{o}C)	yield[b] (%)
1	$AlCl_3$	1.0	benzene	--	90	0
2	$TiCl_4$	1.0	benzene	--	90	0
3	TsOH	1.0	benzene	--	90	0
4	HOTf	1.0	benzene	--	90	20[c]
5	HOTf	5.0	benzene	--	90	96
6	HOTf	5.0	DCE	5.0	90	78[c]
7	**HOTf**	**5.0**	**DCE**	**5.0**	**100**	**94**
8	HOTf	5.0	$MeNO_2$	5.0	100	<10
9	HOTf	5.0	DCE	2.0	100	83
10	HOTf	5.0	DCE	1.0	100	54

[a] reaction was conducted in 0.42 mmol scale in 1.0 mL of solvent.
[b] Isolated yield [c] incompleted reaction

With these conditions in hand, we proceeded to explore the substrate scope of this methodology (Table 2). The reaction is compatible with olefinic pyridines substituted at the 2, 3, or 4 positions, leading to products **3**-**5** in good yields. However, the reaction with 2-substituted pyridine (**5**) was sluggish and to improve the yield, benzene was used as the solvent. The slow reaction rate is presumably due to the stronger electron withdrawing induced effect by the protonated nitrogen when olefinic pyridine substituted at 2 position over 3 or 4 positions. Pyridines substituted with electron-neutral or rich groups were well tolerated. Both the 4-MeO- and 2-Br-substituted methyl-vinylpyridines generated the corresponding products **6** and **7** in good yields. Electron-deficient pyridines failed to provide the desired products. The steric and electronic effects of nucleophilic arenes on the reaction outcome were then screened. With toluene the product **8** was isolated in excellent yield as a mixture of *para*- and *ortho*-substituted isomers in 8:1 selectivity, favoring the para-substituted product. A similar result was observed with chlorobenzene. In both cases the isomers could be separated carefully by column chromatography affording the *para*-isomeric products of **8** and **9**. The reaction with *m*-xylene exclusively afforded **10** as a single isomer. This result is somewhat surprising as electrophilic aromatic substitution of *m*-xylene typically favors addition adjacent to one of the methyl substituents. In this case the high selectivity for this regioisomer may arise due to the steric effect of the *gem*-dimethyl substituent. With more nucleophilic arenes the reaction could be conducted at room temperature, and good yields were observed. Products **11** and **12** were isolated in 72 and 76% yield, respectively. Electron deficient arenes were unreactive under the reaction conditions.

Table 2. Substrate Scope with Olefinic Pyridines[a]

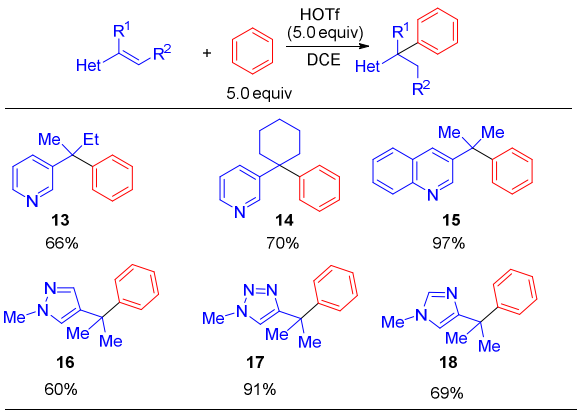


[a]: Conditions: pyridine (0.42 mmol), arene (2.10 mmol), HOTf (2.10 mmol) in 1.0 mL DCE [b]: using pure benzene as solvent [c]: reaction was conducted at rt.

To further demonstrate the efficacy of this transformation, we next explored the possibility of expanding this methodology to different alkyl groups and other heterocycles as summarized in Table 3. The reaction with 3-(but-1-en-2-yl)pyridine led to product **13** in 66% yield. Meanwhile, the hydroarylation of cyclohexenyl pyridine smoothly afforded product **14** in 70% yield, demonstrating that this approach is applicable to other alkyl groups. To broaden the synthetic utility of this method, this approach was then extended to other heterocycles. As expected, the reaction with an olefinic quinoline went smoothly and afforded product **15** in excellent yield. We were delighted to see that this transformation was also applicable to five-membered heterocycles, such as pyrazole, triazole, and imidazole. All of these led to the corresponding products **16**-**18** in good yields. The

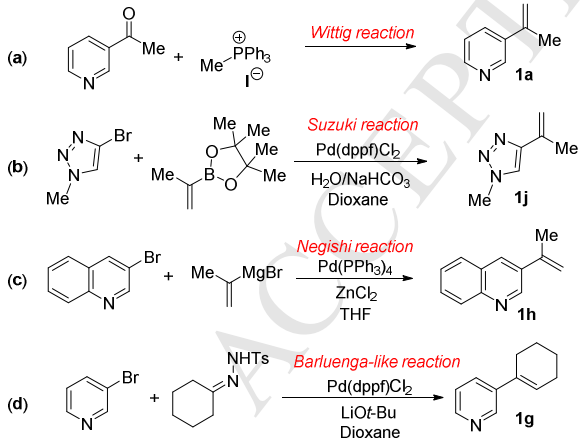
typical approach to construct such structures necessitates a de novo synthesis of the corresponding heterocycle through a multi-step sequence.[7] Unlike the hydroarylation of olefinic pyrazines and quinoxalines, leading to *anti*-Markovnikov addition products,[6c] the reaction with nitrogen-rich heterocycles generated Markovnikov products **16-18** exclusively.

Table 3. Substrate Scope with other heterocycles[a]



[a]: heterocycles (0.42 mmol), arene (2.10 mmol), HOTf (2.10 mmol) in 1.0 mL DCE

Another useful feature of this methodology is that it capitalizes on a broad set of readily available reactants. Indeed, the olefinic aromatic heterocycles employed in this report can be readily synthesized through conventional approaches as listed in Scheme 2. The Wittig reaction, for instance, is a powerful method to synthesize olefinic pyridines,[8] where pyridyl ketones are commercially available. Halogenated heterocycles are widely available and transition-metal catalyzed coupling reactions such as the Suzuki,[9] Negishi[10] and Barluenga-like[11] coupling reactions can also provide fast entry into an assortment of olefinic six- and five-membered heterocycles. Each of these methods was successfully utilized to prepare the substrates found in this work.



Scheme 2. Different approaches to olefinic heterocycles

3. Conclusion

In conclusion, we have developed an expedient approach to *gem*—dialkylbenzyl aromatic heterocycles through the hydroarylation reaction of olefinic heterocycles. A broad range of aromatic heterocycles, including pyridine, quinoline, pyrazole, triazole and imidazole are all highly compatible with this method. In view of the robust nature of the transformation together with the ability to use readily available reactants make this transformation of interest to any field where rapid access to *gem*-dialkyl heterocycles is needed.

4. Experimental section

4.1. General remarks

All reagents were obtained from commercial suppliers and used without further purification, unless otherwise noted. Vinyl heterocycles were synthesized according to published procedures. All solvents used were purchased anhydrous in a DriSolv bottle. Silica gel chromatography was performed using medium pressure CombiFlashRf systems employing Redi Sep Rf Gold silica column, with heptane/EtOAc as eluent. The solvent was evaporated using rotary evaporator at room temperature and 10 mBar. 1H and 13C{1H} NMR characterization data were collected at 300 K on a Bruker AV-500 spectrometer operating at 500.1 and 125.8 MHz (respectively) with chemical shifts reported in parts per million relative to $CHCl_3$ (^{1}H NMR; 7.26 ppm, $^{13}C\{^1H\}$ NMR; 77.23 ppm). Melting point was recorded on Buchi B-545 melting point apparatus. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer and only partial data are provided. High resolution mass spectroscopy (HRMS) was performed on an Agilent (6220) LC-MS TOF using a Xbridge C18 2.5 µm 3.0 X 5.0 mm at 60 °C; ammonium formate: water as mobile phase A1 and 50:50 Methanol:Acetonitrile as mobile Phase B1

4.2 General Procedure for the Preparation of Vinyl Heterocycles

In table 2, products **3**, **8**, **9**, **10**, **11** and **12** were synthesized from starting material **1a** and products **4**, **5**, **6** and **7** were made from starting materials **1b**, **1c**, **1d** and **1e** correspondingly. In table 3, products **13**, **14**, **15**, **16**, **17** and **18** were made from **1f**, **1g**, **1h**, **1i**, **1j** and **1k** correspondingly.

4.2.1 1b, 1c, 1d, 1f were prepared by the Wittig reaction

To a 200 mL round bottle flash was added sodium *tert*-butoxide (1.3 equiv), followed by the addition of 50 mL anhydrous THF, the mixture was stirred until all base was dissolved. Methyltriphenylphosphonium iodide (1.2 equiv) was added in one port and the heterogeneous solution was stirred at rt for 30 mins. Pyridyl ketones (1.0 equiv) were added slowly and the mixture was stirred at rt overnight. The mixture was quenched with water and extracted with ether twice. The combined organic layer was dried ($MgSO_4$) and filtered, concentrated to provide some oil mixed with powder. The crude material was then distilled by Kugelrohr apparatus at 10 mBar with temperature ranging from 50-100 °C to afford the product as colorless liquid. Characterization of unreported **1d**, **1f** is listed below:

4.2.1.1 2-bromo-3-(prop-1-en-2-yl)pyridine (**1d**): Colorless oil (0.331 g, 67% yield). ^{1}H NMR ($CDCl_3$): δ 8.27 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.47 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.23 (dd, *J* = 7.5, 4.7 Hz, 1H), 5.27-5.30 (m, 1H), 5.00 (s, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 148.6, 143.8, 141.9, 141.4, 137.9, 122.8, 117.7, 23.2;

IR(film): 1551, 1380, 1047, 904, 806, 747, 650 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For C_8H_9BrN: 197.9913 Found: 197.9942.

4.2.1.2 3-(but-1-en-2-yl)pyridine (**1f**): Colorless oil (0.39g, 79% yield). ^1H NMR ($CDCl_3$): δ 8.66 (s, 1H), 8.49 (d, *J* = 4.5 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.24 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.31 (s, 1H), 5.15 (s, 1H), 2.50 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 148.5, 147.6, 147.2, 137.0, 133.4, 123.2, 112.8, 28.0, 12.8; IR(film): 2968, 1629, 1410, 1022, 897, 814, 717, 623 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_9H_{12}N$: 134.0964 Found: 134.0961.

4.2.2 1e, 1i, 1j, 1k were prepared by the Suzuki reaction

To a 50 mL round bottle flask was added 1,1'-Bis(diphenylphosphino)ferrocenedichloro Palladium(II) (0.1 equiv), bromide (1.0 equiv) and vinylboronic acid pinacol ester (2.0 equiv) in 20 mL dioxane. The mixture was degassed for 5 mins, and sodium carbonate aqueous solution (2.0 M, 10 equiv) was added. The mixture was then heated to 85 ^oC for 14h. After cooled to rt, the reaction mixture was filtered through a short celite pad and washed with EtOAc. The organic solution was concentrated under reduced pressure and the residue was loaded into combi flush for purification to afford the product as oil.

4.2.2.1 4-methoxy-2-(prop-1-en-2-yl)pyridine (**1e**): Colorless oil (139 mg, 47% yield). ^1H NMR ($CDCl_3$): δ 8.41 (d, *J* = 5.7 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 5.7, 2.4 Hz, 1H), 5.85 (s, 1H), 5.28 (s, 1H), 3.85 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.3, 160.1, 150.3, 143.2, 115.9, 108.1, 106.4, 55.2, 20.7; IR(film): 2972, 1586, 1563, 1300, 1233, 1038, 868, 815 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_9H_{12}NO$: 150.0913. Found: 150.0912.

4.2.2.2 1-methyl-4-(prop-1-en-2-yl)-1H-pyrazole (**1i**): Colorless oil (543 mg, 90% yield). ^1H NMR ($CDCl_3$): δ 7.56 (d, *J* = 2.8 Hz, 1H), 7.34 (d, *J* = 2.8 Hz, 1H), 5.17 (s, 1H), 4.82 (s, 1H), 3.85 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 136.6, 135.0, 126.9, 124.3, 108.7, 39.0, 21.9; IR(film): 2975, 2941, 1635, 1451, 1377, 1240, 1147, 984, 874, 850, 716 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_7H_{11}N_2$: 123.0917. Found: 123.0915.

4.2.2.3 1-methyl-4-(prop-1-en-2-yl)-1H-1,2,3-triazole (**1j**): Colorless oil (390 mg, 94% yield). ^1H NMR ($CDCl_3$): δ 7.48 (s, 1H), 5.70 (d, *J* = 0.7 Hz, 1H), 5.10 (t, *J* = 1.6 Hz, 1H), 4.09 (s, 3H), 2.14 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 149.1, 133.7, 120.7, 112.5, 36.7, 20.8; IR(film): 3132, 2919, 1641, 1454, 1221, 1056, 1037, 893, 809, 717 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_6H_{10}N_3$: 124.0869. Found: 124.0869.

4.2.2.4 1-methyl-4-(prop-1-en-2-yl)-1H-imidazole (**1k**): Colorless oil (136 mg, 22% yield). ^1H NMR ($CDCl_3$): δ 7.36 (s, 1H), 6.82 (s, 1H), 5.64 (s, 1H), 4.89 (s, 1H), 3.64 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 143.6, 137.8, 136.2, 116.5, 109.4, 33.4, 20.4; IR(film): 2943, 1635, 1493, 1232, 1130, 977, 884, 828, 618 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_7H_{11}N_2$: 123.0917. Found: 123.0918.

4.2.3 3-(prop-1-en-2-yl)quinoline 1h was prepared by the Negeshi reaction

In a 50 mL oven-dried round bottle flask with $ZnCl_2$ (3.2 mL of 1.9 M in methyltetrahydrofuran, 6.2 mmol, 3.0 equiv) was added isopropenylmagnesium bromide solution (12.0 mL of 0.5 M in THF, 6.2 mmol, 3.0 equiv) at 0 ^oC slowly. The reaction mixture was warmed up to room temperature and was stirred for additional 30 mins. In another 100 mL oven-dried round bottle flask was added 3-bromoquinoline (416 mg, 2.0 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (119 mg, 0.05 equiv) in 4 mL THF. After degassed with N_2 for 5 mins, the mixture was then heated to 60 ^oC. The zincate solution was transferred into the bromide solution slowly through cannula. The reaction was kept at 60 ^oC for addition 2h. After cooling down to rt, the reaction was quenched with NH_4Cl solution, extracted by EtOAc (15 mL three times). The organic layers were combined, dried over $MgSO_4$ and filtered. The organic solution was then concentrated under reduced pressure and the residue mixture was loaded into combi flush for purification) to afford the product as colorless oil (286 mg, 85% yield). The analytical data was consistent with the reported literature.[12]

4.2.4 3-(cyclohex-1-en-2-yl)pyridine 1g was prepared by the Barluenga-like reaction

To a 100 ml oven-dried round bottle flask was added N'-cyclohexylidene-4-methylbenzenesulfonohydrazide (3.79 g, 14.2 mmol, 1.0 equiv) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (388 mg, 0.475 mmol, 0.05 equiv) in 50 ml dioxane. The reactions were evacuated and purged with N_2 three times lithium *tert*-butoxide (1.71 g, 20.9 mmol, 2.2 equiv) was added followed by the addition of 3-bromopyridine (1.5 g, 9.49 mmol, 1.0 equiv). The reactions were evacuated and purged with N_2 for additional twice and was heated at 90 ^oC overnight. After cooling down to rt, the reaction mixture was filtered through celite and washed with ethyl acetate. The solvent was evaporated under reduced pressure and the residue was loaded into combi flush for purification by hexane/EtOAC to afford the product as yellowish oil (712 mg, 47%). The analytical data was consistent with the reported literature.[13]

4.3 General Procedure for the Synthesis of *gem*-Dialkylbenzyl Heterocycles

To a one draw vial with olefin (1.0 equiv), arenes (5.0 equiv) in dichloroethane (1.0 mL, c = 0.42 M) was added triflic acid (315 mg, 2.1 mmol, 5.0 equiv). The mixture was then heated to 100 ^oC for 20h. After cooling down to rt, the reaction mixture was quenched with 4N NaOH solution at 0 ^oC. The mixture was extracted by ether for four times. The organic layers were combined and then evaporated by flushing with N_2. The residue was then loaded into combi flush for purification by heptane/EtOAc to generate the product as an oil.

4.3.1 3-(2-phenylpropan-2-yl)pyridine (**3**): Colorless oil (77.8 mg, 94% yield). ^1H NMR ($CDCl_3$): δ 8.47 (d, *J* = 2.5 Hz, 1H), 8.35 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.41 (ddd, *J* = 8.0, 2.5, 1.6 Hz, 1H), 7.17-7.23 (m, 2H), 7.07-7.16 (m, 4H), 1.63 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.4, 148.6, 147.2, 145.9, 134.6, 128.4, 126.8, 126.2, 123.0, 41.9, 30.5; IR(film): 2969, 1476, 1413, 1023, 763, 698 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{14}H_{16}N$: 198.1277. Found: 198.1273.

4.3.2 4-(2-phenylpropan-2-yl)pyridine (**4**): Colorless oil (70.4 mg, 85% yield). ^{1}H NMR ($CDCl_3$): δ 8.49-8.52 (m, 2H), 7.28-7.35 (m, 2H), 7.21-7.26 (m, 3H), 7.14-7.17 (m, 2H), 1.70 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 159.7, 149.8, 148.8, 128.4, 126.8, 126.3, 122.2, 43.0, 30.1; IR(film): 2971, 1595, 1409, 1071, 822, 764, 732, 698, 579 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{14}H_{16}N$: 198.1277. Found: 198.1271.

4.3.3 2-(2-phenylpropan-2-yl)pyridine (**5**): Colorless oil (74.6 mg, 90% yield). ^{1}H NMR ($CDCl_3$): δ 8.61 (dd, *J* = 5.1, 2.2 Hz, 1H), 7.56 (td, *J* = 7.9, 1.9 Hz, 1H), 7.27-7.34 (m, 4H), 7.19-7.24 (m, 1H), 7.08-7.13 (m, 2H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.8, 149.7, 148.6, 136.1, 128.3, 126.8, 125.9, 121.8, 120.9, 45.7, 29.7; IR(film): 2970, 1585, 1427, 992, 787, 747, 698, 573 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{14}H_{16}N$: 198.1277. Found: 198.1279.

4.3.4 2-bromo-3-(2-phenylpropan-2-yl)pyridine (**6**): Colorless oil (97.6 mg, 84% yield). ^{1}H NMR ($CDCl_3$): δ 8.29 (dd, *J* = 4.6, 1.9 Hz, 1H), 7.97 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.34 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.27-7.31 (m, 2H), 7.19-7.24 (m, 1H), 7.11-7.16 (m, 2H), 1.81 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 148.4, 147.6, 145.3, 144.0, 136.6, 128.4, 126.3, 125.9, 122.6, 44.0, 30.1; IR(film): 2970, 1555, 1381, 1114, 1039, 908, 727, 697 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{14}H_{15}BrN$: 276.0382. Found: 276.0379.

4.3.5 4-methoxy-2-(2-phenylpropan-2-yl)pyridine (**7**): Colorless oil (80.0 mg, 84% yield). ^{1}H NMR ($CDCl_3$): δ 8.41 (d, *J* = 5.6 Hz, 1H), 7.25-7.30 (m, 4H), 7.18 (td, *J* = 6.7, 1.9 Hz, 1H), 6.61-6.65 (m, 2H), 3.75 (s, 3H), 1.73 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.5, 166.0, 150.0, 149.5, 128.3, 126.7, 126.0, 108.2, 106.8, 55.1, 45.7, 29.6; IR(film): 2968, 1589, 1566, 1475, 1301, 1039, 698 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{15}H_{18}NO$: 228.1383. Found: 228.1377.

4.3.6 3-(2-(p-tolyl)propan-2-yl)pyridine (**8**): Colorless oil (85.0 mg, 96% yield). ^{1}H NMR indicated the regiomeric ratio was 8:1 favored the *para*-isomer. Partial separation was achieved by using DCM/EtOAc as eluent. ^{1}H NMR ($CDCl_3$): δ 8.55 (d, *J* = 2.4 Hz, 1H), 8.43 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.0, 2.5, 1.6 Hz, 1H), 7.17 (ddd, *J* = 8.1, 4.7, 0.8 Hz, 1H), 7.10 (s, 4H), 2.32 (s, 3H), 1.70 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 148.6, 147.2, 146.5, 146.1, 135.7, 134.6, 129.1, 126.7, 123.0, 41.6, 30.6, 21.0; IR(film): 2963, 1510, 1466, 1243, 1029, 753, 636 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{15}H_{18}N$: 212.1434. Found: 212.1428.

4.3.7 3-(2-(4-chlorophenyl)propan-2-yl)pyridine (**9**): Colorless oil (90.2 mg, 93% yield). ^{1}H NMR indicated the regiomeric ratio was 5:1 favored the *para*-isomer. Partial separation was achieved by reverse phase chromatography with CH_3CN/water as eluent. ^{1}H NMR ($CDCl_3$): δ 8.54 (s, 1H), 8.44 (d, *J* = 4.7 Hz, 1H), 7.48 (dt, *J* = 8.1, 1.7 Hz, 1H), 7.22-7.27 (m, 2H), 7.19 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.11-7.16 (m, 2H), 1.68 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 147.7, 147.6, 146.6, 146.0, 135.5, 132.2, 128.6, 128.3, 123.5, 41.8, 30.5; IR(film): 2969, 2926, 1490, 1414, 1096, 1012, 828, 714 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{14}H_{15}ClN$: 232.0888. Found: 232.0893.

4.3.8 3-(2-(3,5-dimethylphenyl)propan-2-yl)pyridine (**10**): Colorless oil (68.3 mg, 72% yield). ^{1}H NMR ($CDCl_3$): δ 8.55 (d, *J* = 2.4 Hz, 1H), 8.43 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.50 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1H), 7.18 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1H), 6.85 (s, 1H), 6.83 (s, 2H), 2.27 (s, 6H), 1.69 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.3, 148.6, 147.1, 146.1, 137.7, 134.5, 127.8, 124.7, 123.0, 41.6, 30.6, 21.6; IR(film): 1404, 914, 843, 733, 703 cm^{-1}; HRMS (ESI/[M+Na]+) calcd. For $C_{16}H_{19}NNa$: 248.141, found 248.1421.

4.3.9 3-(2-(4-methoxyphenyl)propan-2-yl)pyridine (**11**): Colorless oil (68.9 mg, 72% yield). ^{1}H NMR indicated the regiomeric ratio was 1.2:1 favored the *para*-isomer. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, *J* = 2.4 Hz, 1H), 8.46 (d, *J* = 2.4 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.37 (d, *J* = 4.8 Hz, 1H), 7.43-7.51 (m, 3H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.11-7.20 (m, 4H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.77-6.85 (m, 3H), 3.79 (s, 3H), 3.36 (s, 3H), 1.69 (12H); ^{13}C NMR ($CDCl_3$) δ 157.9, 157.5, 148.6, 147.5, 147.1, 146.2, 146.1, 141.6, 136.9, 134.6, 133.3, 129.6, 128.2, 127.8, 126.6, 123.0, 122.8, 120.6, 113.7, 112.5, 55.4, 55.1, 41.3, 40.7, 30.7, 29.3; IR(film): 2966, 1510, 1413, 1242, 1182, 1024, 807, 753, 714 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{15}H_{18}NO$: 228.1383. Found: 228.1377.

4.3.10 3-(2-(3,4-dimethoxyphenyl)propan-2-yl)pyridine (**12**): Colorless oil (82.1 mg, 76% yield). ^{1}H NMR ($CDCl_3$): δ 8.55 (d, *J* = 2.4 Hz, 1H), 8.43 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 8.1, 4.7 Hz, 1H), 6.80 (s, 2H), 6.65 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 1.69 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 148.8, 148.3, 147.5, 147.1, 146.1, 142.0, 134.7, 123.1, 118.7, 110.9, 110.8, 56.01, 55.99, 41.6, 30.7; IR(film): 2966, 1588, 1509, 1463, 1411, 1253, 1153, 1024, 807, 715, 652 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{16}H_{10}NO_2$: 258.1489. Found: 258.1488.

4.3.11 3-(2-phenylbutan-2-yl)pyridine (**13**): Colorless oil (58.5 mg, 66% yield). ^{1}H NMR ($CDCl_3$): δ 8.53 (d, *J* = 2.5 Hz, 1H), 8.45 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.48 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1H), 2.28-2.33 (m, 2H), 7.18-7.24 (m, 4H), 2.19 (q, *J* = 7.4 Hz, 2H), 1.67 (s, 3H), 0.78 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.2, 148.3, 147.1, 145.0, 135.2, 128.3, 127.5, 126.1, 123.0, 45.5, 33.9, 26.8, 9.2; IR(film): 2969, 1476, 1413, 1022, 760, 697 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{15}H_{18}N$: 212.1434. Found: 212.1427.

4.3.12 3-(1-phenylcyclohexyl)pyridine (**14**): White powder (69.8 mg, 70 % yield), (mp: 148-150 ^{o}C)^{1}H NMR ($CDCl_3$): δ 8.56 (d, *J* = 2.2 Hz, 1H), 8.49 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.59 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.32-7.38 (m, 2H), 7.21-7.30 (m, 4H), 2.60-2.71 (m, 2H), 2.02-2.14 (m, 4H), 1.62-1.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 149.0, 147.6, 147.2, 142.5, 134.3, 128.5, 126.9, 126.2, 123.5, 44.0, 41.7, 34.43, 34.36; IR(film): 2924, 2851, 1423, 1265, 735, 700 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{17}H_{20}N$: 238.1590. Found: 238.1592.

4.3.13 3-(2-phenylpropan-2-yl)quinolone (**15**): Colorless oil (100.4 mg, 97% yield). ^{1}H NMR ($CDCl_3$): δ 8.72 (d, *J* = 2.3 Hz, 1H), 8.07-8.11 (m, 2H), 7.82 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.70 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.56 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.21-7.35 (m, 5H), 1.84 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 151.7, 149.0, 146.4, 143.2, 131.7, 129.1, 128.9, 128.4, 127.82, 127.79,

126.8, 126.7, 126.2, 42.0, 30.5; IR(film): 2968, 1493, 1370, 1236, 1084, 905, 750, 698, 557 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{18}H_{18}N$: 248.1434. Found: 248.1429.

4.3.14 1-methyl-4-(2-phenylpropan-2-yl)-1H-pyrazole (**16**): Colorless oil (50.5 mg, 60 % yield). ^1H NMR ($CDCl_3$): δ 7.25-7.34 (m, 5H), 7.15-7.20 (m, 1H), 7.07 (s, 1H), 3.86 (s, 3H), 1.64 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 150.2, 137.4, 132.7, 128.2, 127.8, 126.3, 125.9, 39.0, 37.1, 31.4; IR(film): 2966, 1442, 1203, 986, 761, 699, 681 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{13}H_{17}N_2$: 201.1386. Found: 201.1386.

4.3.15 1-methyl-4-(2-phenylpropan-2-yl)-1H-1,2,3-triazole (**17**): Colorless oil (76.8 mg, 91 % yield). ^1H NMR ($CDCl_3$): δ 7.34 (d, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.10 (s, 1H), 4.02 (s, 3H), 1.76 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 157.3, 148.7, 128.3, 126.3, 126.2, 121.4, 38.3, 36.6, 29.9; IR(film): 2969, 1444, 1196, 763, 698 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{12}H_{16}N_3$: 202.1339. Found: 202.1345.

4.3.16 1-methyl-4-(2-phenylpropan-2-yl)-1H-imidazole (**18**): Colorless oil (57.8 mg, 69 % yield). ^1H NMR ($CDCl_3$): δ 7.34-7.39 (m, 3H), 7.24-.28 (m, 2H), 7.14-7.18 (m, 1H), 6.51 (d, *J* = 1.4 Hz, 1H), 3.60 (s, 3H), 1.69 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 151.9, 149.6, 137.2, 128.0, 126.4, 125.7, 115.7, 39.4, 33.3 29.6; IR(film): 2966, 1499, 1225, 1200, 970, 762, 697, 623 cm^{-1}; HRMS (ESI/[M+H]+) calcd. For $C_{13}H_{17}N_2$: 201.1386. Found: 201.1383.

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Supplementary Material

Supplementary data (Supplementary data comprising ^1H and ^{13}C NMR for all new compounds was given and it can be found in the online version) related to this article can be found.

Supporting Information for:

Expedient Synthesis of *gem*-Dialkylbenzyl Heterocycles through Olefinic Hydroarylation

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