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Iron-Catalysed Alkylation of 2-Methyl and 4-Methyl azaarenes with Alcohols via C-H Bond Activation

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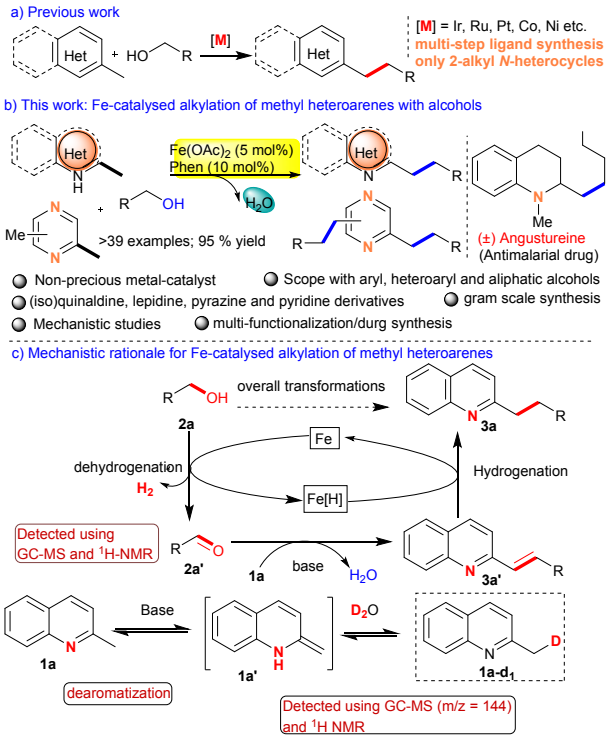
The first Fe-catalysed alkylation of 2-methyl and 4-methyl-azaarenes with a series of alkyl and hetero-aryl alcohols is reported (>39 examples and up to 95% yield). Multi-functionalisation of pyrazines and synthesis of anti-malarial drug (±) Angustureine significantly broadens the scope of this methodology. Preliminary mechanistic investigation, deuterium labeling and kinetic experiments including trapping of the enamine intermediate 1a' are of special highlights.

N-Heteroaromatics and their derivatives are ubiquitous in various important pharmaceuticals, bioactive compounds and significantly used as lifesaving drugs.[1] Therefore, metal-catalysed functionalization of C(sp^3)-H bond in such azaarenes enables access to valuable *N*-hetero aromatics.[2] Nevertheless, conventional pre-functionalised alkyl halides, carbonates and esters are utilised for such alkylation of *N*-heteroaromatics and generates undesired side waste. In general, selective functionalization of C(sp^3)-H bond associated with high energy barriers. Thus, often metal-catalysed alkylation of such C-H bonds were performed involving directing group assistance in combination with activated olefins or related derivatives.[3] Hence, development of an atom-economic alkylation process for C(sp^3)-H bond in *N*-heteroaromatics following sustainable technology is a challenging goal.[4] Notably, in terms of sustainability, recent years witnessed the applications of bio-mass derived renewable alcohols as a promising coupling partner for alkylation process. Such metal-catalysed hydrogen borrowing (HB) approach has been well documented for the construction the new C-X (X = C, N etc.) bonds and generates water as sole by-product.[5]

Pioneering study by Kempe on Ir-catalysed alkylation of methyl *N*-heteroaromatics using alcohols is noteworthy.[6a] Thereafter, other precious metal-based catalysts have been explored for such alkylation (Ir-, Ru-, and Pt).[6b-h] Thus, replacement of precious and expensive metal-base catalysts with earth abundant and inexpensive metals attracted significant attention in catalytic research.[7] Recently, a few examples based on non-precious metal catalysts were reported for alkylation of 2-methyl *N*-heteroaromatics using alcohols.[8] Nevertheless, often applications of pincer-based PN_5P or NNN-ligands system is the key for success. Importantly, such processes are expensive and required multi-step ligand synthesis (Scheme 1a). However, to the best of our knowledge iron-catalysed alkylation of primary alcohols with 2-methyl or 4-methyl *N*-heteroaromatics yet not established.[8] Notably, iron is non-toxic, most earth-abundant, inexpensive metal and found in variable biological systems. Therefore, application of iron-catalysts for crucial organic transformations fascinated significantly.[9]



Scheme 1: (a) Previous reports. (b) Proposed Fe-catalysed alkylation of *N*-heteroarenes with alcohols. (c) Mechanistic proposal.

Recently, we have started a program to explore the potential role of non-precious metal-catalysts (Ni-, Mn-, and Fe-) for sustainable organic transformations.[10] In this direction, we have studied Ni-, and Fe-catalysed synthesis of *E*-selective olefins involving alkyl *N*-heteroarenes with primary alcohols.[11] Notably, during mechanistic studies for the Ni-catalysed alkylation of *N*-heteroarenes with alcohols, we envisioned the potential role of the Ni-H species for the hydrogenation of the intermediate **3a'** (Scheme 1c). Therefore, 10 mol % $NiBr_2$ and excess (50 mol %) 1,10-phenanthroline was the key for selective alkylation.[12] Again, we witnessed the diminished reactivity for heteroaryl alcohols, cyclic alkyl alcohols, and even with

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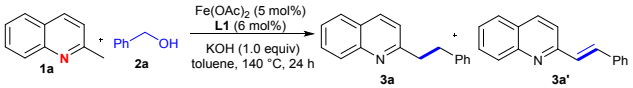
lepidine derivatives.[12] Interestingly, the present strategy report the first example of inexpensive Fe-catalysed route (5 mol % cat. and 10 mol % ligand) for chemo-selective alkylation of methyl *N*-hetero aromatics, such as, quinaldine, lepidine, pyridines, pyrazines, isoquinolines including benzimidazole and quinoxaline with a series of alkyl and hetero-aryl alcohols (Scheme 1b).

Table 1. Fe-catalysed alkylation of 2-methylquinoline with alcohol[a]



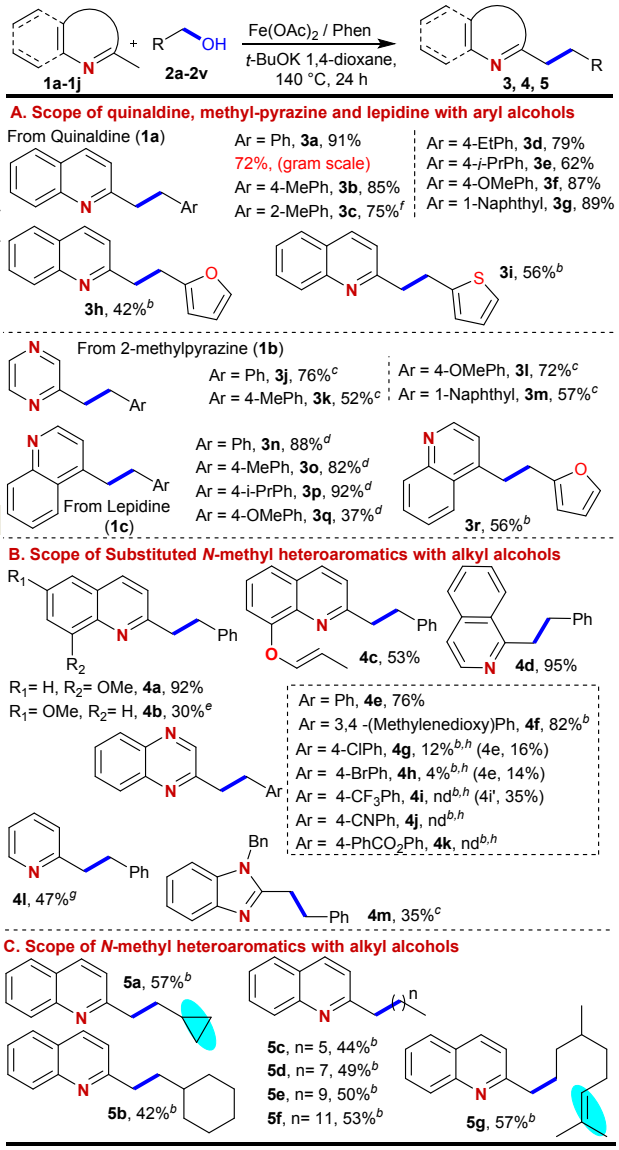
Entry	Deviation from the above	Conv. (%)[b]	
		3a	**3a'**
1	-	71	29
2	$Fe(acac)_3$	6	0
3[c]	$Fe_2(CO)_9$	16	35
4	$FeCl_2$	10	70
5	**L3** instead of **L1**	10	55
6	**L5** instead of **L1**	40	60
7	1,4-dioxane	75	25
8	1,4-dioxane, *t*-BuOK	76	14
9	1,4-dioxane, *t*-BuONa	21	11
10	1,4-dioxane, *t*-BuOK, **L1** (10 mol%)	**93 (91)**	3
11	no Fe-cat., no **L1**, *t*-BuOK, 1,4-dioxane	2	-
12	no base, 1,4-dioxane	0	-

Reaction conditions: [a]**1a** (0.25 mmol), **2a** (0.50 mmol), $Fe(OAc)_2$ (0.0125 mmol), phen (0.025 mmol), *t*-BuOK (0.25 mmol) in 1,4-dioxane (1.0 mL) in a pressure tube under N_2 atmosphere at 140 °C (oil bath) for 24 h. [b]Isolated yield, [c]$Fe_2(CO)_9$ (2.5 mol%), phen (3.0 mol%) were used. **L1** = 1,10-phenanthroline. **L2** = 2,9-dimethyl 1,10- phenanthroline. **L3** = bipyridine. **L4** = 4,4' -dimethylbipyridine. **L5** = 2,2'-biquinoline. Conversions were calculated based on **1a.**

Primarily, we systematically investigated the model reaction involving 2-methylquinoline (**1a**) with benzyl alcohol (**2a**) using different Fe-catalysts (Table 1, entries 1-4). To our delight, Fe(II) acetate (5 mol%) and 1,10-phenanthroline **L1** (6 mol%) gave 71% isolated yield of **3a**, when using KOH (1.0 equiv.) as a base. Interestingly, olefin **3a'** was also detected in the GC-MS analysis (Table 1, entry 1 and SI Table S1). Further, to improve the product yields and selectivity of **3a**, electronically different nitrogen-based ligands **L2-L5** were tested and proved less efficient (Table 1, entries 5-6 and SI Table S2). Next, influence of different non-polar or polar solvents (*p*-xylene, 1,4-dioxane, *N*, *N*-dimethyl acetamide and *t*-amyl alcohol) were examined and found 1,4-dioxane as promising solvent for the alkylation process (Table 1, entry 7 and SI Table S3). Thereafter, application of different bases (*t*-BuOK, *t*-BuONa, NaOH, KOH and K_2CO_3) in 1,4-dioxane resulted in up to 76% conversion to **3a** (Table 1, entries 8-9 and SI Table S4). At this point, we realized the potential role of the ligand **L1** to control the product selectivity. As expected, an increment to 10 mol% of **L1** gave almost quantitative yield of **3a** (Table 1, entry 10 and SI Table S5). Alkylation reaction using lower catalyst loading resulted albeit with poor product yield. Control experiments, revealed the significant role of the individual component and poor alkylation product observed in case of lower catalyst and base loading (entries 11-12, SI Tables S1-S5). Notably, we observed benzaldehyde formation in ^{1}H-NMR and GC-MS analysis of the crude reaction mixture (Scheme 1c).

Next, using the standard conditions of (Table 1, entry 10), a series of primary alcohols were examined with quinaldine, pyrazine and lepidine in good to excellent yields (Scheme 2). Initially, when 2-methylquinoline **1a** was employed with benzyl alcohols (**2b**, **2d-f**) bearing *p*-methyl, *p*-ethyl, *p-iso*-propyl and *p*-methoxy substituents, resulted the desired alkylated products **3b** and **3d-3f** in up to 87% yields (Scheme 2). Importantly, sterically hindered *o*-methyl benzyl alcohol **2c** and 1-naphthylmethanol **2g** reacted smoothly with **1a**, **3c** and **3g** were obtained in 85-89% isolated yields respectively.

Scheme 2: Synthesis of chain-elongated heteroarenes[a]



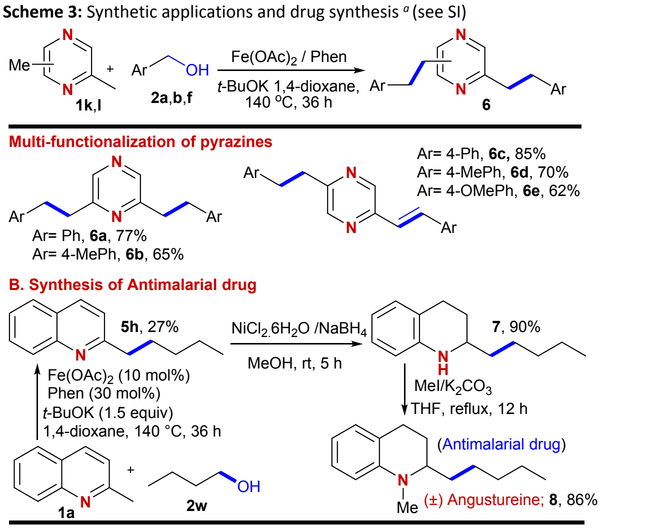
Reaction Conditions: [a]**1a** (0.25 mmol), primary alcohol **2a** (0.50 mmol), $Fe(OAc)_2$ (0.0125 mmol), phen (0.025 mmol), *t*-BuOK (0.25 mmol) using 1,4-dioxane (1.0 mL) in pressure tube under N_2 atmosphere at 140 °C in a pre-heated oil bath for 24 h. [b]**2** (0.75 mmol), $Fe(OAc)_2$ (0.025 mmol), phen (0.075 mmol), *t*-BuOK (0.375 mmol), 36 h. [c]36 h. [d]*t*-BuOK (0.25 mmol), 24 h. [e]*t*-BuOK (0.375 mmol), 36 h. [f] **2** (0.75 mmol), $Fe(OAc)_2$ (0.025 mmol), phen (0.075 mmol), *t*-BuOK (0.375 mmol), 36 h, 150 °C. [g]2-methylpyridine *N*-oxide is used (0.25 mmol), Fe(OAc)2 (0.025 mmol), phen (0.075 mmol), *t*-BuOK (0.50 mmol), 36 h. [h]GC-MS conversion based on **1h**.

Notably, more challenging, furan-2yl-methanol, **2h** and thiophene-2yl-methanol **2i** coupled with **1a** and transformed into the bis-heteroarylated alkanes **3h-3i** in 42-56% yields (Scheme 2). Further, when using, 2-methylpyrazine, **1b** as coupling partner with electronically different benzyl alcohols (**2a,b** and **2f,g**), the desired alkylated pyrazines were obtained in up to 76% yields (**3j-3m**, Scheme 2). Remarkably, 4-methylquinoline (lepidine, **1c**) also participated efficiently with different aryl and heteroaryl alcohols and transformed into the desired 4-alkylatedquinolines **3n-3r**, in up to quantitative yields (up to 92%, Scheme 2).

After having excellent reactivity, we further extended the alkylation process using electronically different alkyl *N*-heteroaromatics with

benzyl alcohols (Scheme 2). To our delight, 8-methoxyquinaldine **1d**, afforded almost quantitative yield (91%) to **4a**. However, the reaction with 6-methoxyquinaldine **1e**, was sluggish and resulted acceptable yield to **4b**. Whereas, 8-alkoxyquinaldine **1f** furnished the alkylated product **4c** in moderate yield (53%, Scheme 2). Notably, 1-methylisoquinoline **1g** and 2-methylquinoxaline **1h**, efficiently transformed into the products **4d-4e** in 76-95% yield respectively (Scheme 2). Importantly, 3,4-methylenedioxybenzyl alcohol **2j,** gave the desired functionalised product **4f** in 82% yield (Scheme 2). However, benzyl alcohols (**2k**-**2o**) bearing chloro, bromo, trifluoromethyl, nitrile and phenyl ester functionalities did not result the desired products (**4g-4k**) and only de-halogenated products or intermediated olefin was detected in the GC-MS analysis. Interestingly, 2-methyl-pyridine did not participate for the alkylation process under the standard conditions. However, 2-methylpyridine *N*-oxide **1i**, resulted the deoxygenated alkylated pyridine **4l** in moderate yield (47%, Scheme 2). Again, 2-benzyl-benzo[d]azole **1f**, efficiently participated and resulted the interesting heteroarene **4m** in 35% yield (Scheme 2).

Scheme 3: Synthetic applications and drug synthesis [a] (see SI)

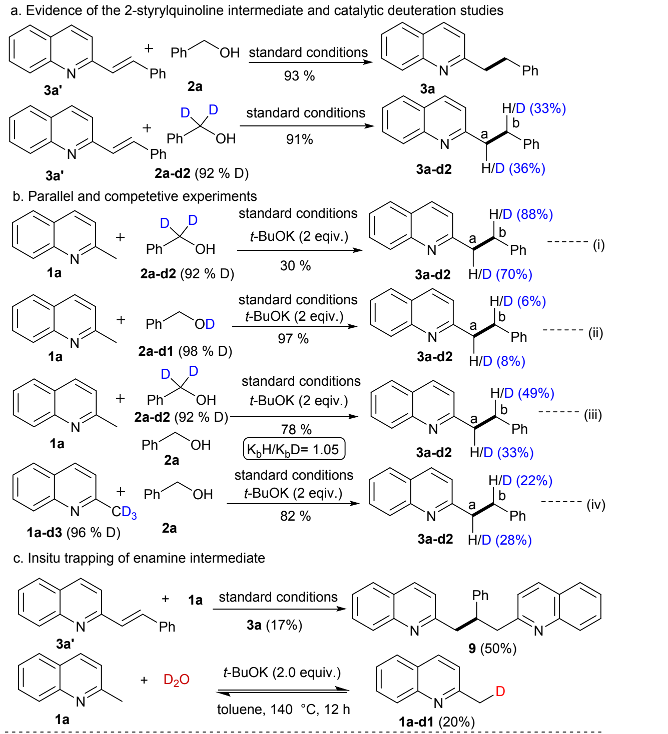


Next we studied the alkylation of **1a** with more challenging cyclic and acyclic alkyl alcohols (Scheme 2). To our delight, reactions of **1a** with cyclopropylmethanol **2p**, and cyclohexylmethanol **2q**, converted into the desired alkylated derivatives **5a-5b** in moderate yields **(**42-53%, Scheme 2). Gratifyingly, acyclic linear C4-C12 alkyl alcohols, **2r**-**2u** and **2w** smoothly participated with **1a** and transformed into the chain-elongated quinolines in up to 53% isolated yields (**5c**-**5f** and **5h**, Schemes 2-3). Similarly, citronellol **2v** (a natural acyclic monoterpenoid) chemo-selectively alkylated with **1a** and resulted in 57% yield of **5g** without significantly affecting the olefinic double bond (Scheme 2).

For a practical application, the catalytic protocol was applied for the one-pot multi-functionalisation of pyrazine derivatives. For instance, 2,6-dimethyl pyrazine **1k**, and 2,5-dimethyl pyrazine **1l**, employed with substituted benzyl alcohols (**2a**-**b** and **2f**) and resulted the interesting bis-alkylated pyrazines in up to 85% yields (**6a**-**e**, Scheme 3). Notably, these bis-functionalised pyrazines widely used in materials applications.[2] A gram scale reaction could be performed using standard conditions and 72% yield of **3a** was obtained (Scheme 2 and ESI, Scheme S8, 1.17 g). For a synthetic application, we made an attempt for the straightforward synthesis of the anti-malarial drug (±) Angustureine **8**. Ni-catalysed hydrogenation followed by *N*-methylation of the alkylated product **5h**, resulted the desired drug **8** in excellent yield (Scheme 3).[1] These examples highlight the importance of the present protocol.

Remarkably, the current protocol is tolerant to quinaldine, lepidine, pyridines, pyrazines, isoquinolines, benzimidazole including quinoxaline. A series of cyclic and acyclic alkyl alcohols, hetero-aryl alcohols, sterically hindered 2-methylbenzyl alcohols including allylic ether and terminal olefin functionalities participated efficiently. However, we observed diminished reactivity in case of benzyl alcohols having halides, nitro and nitrile functionalities including pyridine motif.

Scheme 4: Catalytic and mechanistic studies[a] (see SI)



Thereafter, we focused to gain deeper insight into the reaction mechanism for the alkylation process and a series of deuterium-labelling and control experiments were performed (Scheme 4). At the beginning, 2-styrylquinoline **3a'** was employed with **2a** and **2a-d2** (92% D) under standard conditions and afforded **3a** and **3a-d2** in up to 93% yield. We observed 33-36% deuterium incorporation at **3a-d2** (Scheme 4a and SI, Scheme S5). Further, alkylation of **1a** using **2a-d2** (92% D) or **2a-d1** (98% D), indicated the formation of H/D-scrambled product **3a-d2** in variable yields (Scheme 4bi-ii, SI, Schemes S1-S2). However, in case of **2a-d1** only 6-8% deuterium incorporation indicated the micro-reversible HB process using iron-catalysis.[13] Additionally, a competitive experiment using 1:1 mixture of **2a** and **2a-d2** with **1a** also established the micro-reversible HB transformations (Scheme 4biii and SI, Scheme S3). Notably, the alkylation reaction of **1a-d3** with benzyl alcohol **2a** resulted the formation of **3a-d2** in 82% yield and exhibited 22-28% deuterium incorporation (Scheme 4biv and SI, Scheme S4). These deuterated experimental findings are in agreement for the D/H exchange following hydrogen auto-transfer principle (Scheme 4 and SI, Schemes S1-S5).[13a]

Nevertheless, a series of control experiments were performed using **1a** with 4-methoxybenzaldehyde **2f'** and **2f** in presence and absence of iron-catalyst, revealed the significant role of the Fe-catalyst for the alkylation process (Scheme S11). Moreover, alkylation of the model reaction (Table 1) was monitored using gas chromatography analysis for 22 h and revealed the constant formation of benzaldehyde **2a'** following dehydrogenation of alcohol **2a** (SI, Scheme S7).

Gratifyingly, we have studied the ^{1}H-NMR analysis for the detection of in situ generation of water during alkylation process (SI, Scheme S10). Finally, to determine the rate and order of the reaction, two sets of kinetics experiments were performed and we observed the first order kinetics (SI, Scheme S6).

Based on our initial mechanistic and control experiments, we proposed a possible catalytic cycle in Scheme 1c.[12] Primarily, to establish the involvement of 1**a'**, we proposed the base mediated (de)aromatization of quinaldine **1a** to 1**a'**. For instance, in absence of base, no **3a** was formed (Table 1, entry 12), highlighting the essential role of *t*-BuOK for (de)aromatization of quinaldine. Additionally, when **1a** was reacted with D_2O and *t*-BuOK at 140 °C for 12 h, **1a-d1** was formed in 20% yield (Scheme 4c). Again, to trap the intermediate **1a',** an *in situ* experiment was performed using **1a** with **3a'** and resulted **9** in 50 % yield (Scheme 4c). These, control experiments strongly support the participation of enamine **1a'** (SI, Scheme S9). On the basis of our initial findings and literature report, we anticipated that, initially, alcohol **2a** undergoes dehydrogenation to aldehyde **2a'** catalyzed by iron and transient Fe-H species is formed (Scheme 1c).[9] Afterward, aldehyde coupled with enamine **1a'** to the intermediate **3a'**. Successive hydrogenation of **3a'** by transient Fe-H species gave alkylated product **3a** with the elimination of water (Scheme 1c). Notably, chemo-selective alkylation was achieved when 1,4-dioxane was used as solvent and facilitate the hydrogenation of **3a'** by Fe-H species.[11a] Nevertheless, Meerwein-Ponndorf mechanism for such process is another possibility.[13b]

In summary, we have reported an operationally simple and cost-efficient iron-catalysed system for the alkylation of 2-methyl and 4-methylazaarenes with alcohols. A series of substituted *N*-hetero-arenes could efficiently participated with various cyclic and acyclic alkyl alcohols, hetero-aryl alcohols having allylic and terminal olefin functionalities. Multi-functionalisation of pyrazines, synthesis of anti-malarial drug (±) Angustureine including initial mechanistic investigation, kinetic studies and trapping of the enamine intermediate **1a'** are of special highlights.

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Conflicts of interest

There are no conflicts to declare.

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Graphical Abstract:

Iron-catalysed alkylation of methylazaarenes with primary alcohols is presented. The catalytic protocol is highly selective for alkylation process and generates water as by-product.