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Lewis Acid-Catalyzed C(sp^3)-C(sp^3) Bond Forming Cyclization Reactions for Synthesis of Tetrahydroprotoberberine Derivatives

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Abstract. An efficient Lewis acid-catalyzed C(sp^3)-C(sp^3) bond forming annulation reaction has been developed. This strategy serves as a new method for the facile synthesis of tetrahydro-5H-isoquinolino[2,1-g][1,6]naphthyridine derivatives. A wide range of 2-methylquinoline-3-carbaldehydes and 1,2,3,4-tetrahydroisoquinolines can be applied for this process to afford structurally diverse tetrahydroprotoberberine derivatives in excellent yields.

Keywords: annulation; azaarene activation; C(sp^3)-C(sp^3) bond formation; Lewis acid catalysis; tetrahydroprotoberberine derivatives

The development of new, efficient synthetic methods for construction of natural product like skeletons has been a highly active research topic in synthesis and drug discovery. Tetrahydroprotoberberines (THPBs),[1] containing the 'privileged' quinolizine core, possess a broad range of biological activities such as antifungal,[2] antimicrobial,[3] antiepileptic,[4] anti-inflammatory,[5] antihypertensive,[6] antiviral,[7] and antitumor[8] actions. Therefore, methods enabling facile preparation of the molecular framework are highly valuable. The conventional synthetic protocols include the Bischler–Napieralski[9] and Pictet–Spengler reactions.[10] Recently, THPBs derivatives containing CH_2 bioisostere N, O and S atoms have been synthesized *via* the reaction of tetrahydroisoquinolines with 2-substituted benzaldehydes, mainly contributed by Seidel and coworkers (Figure 1, eq 1).[11] In these processes, these 2-substituted benzaldehydes containing highly nucleophilic functional groups NH_2, OH and SH were used for effective transformations. More recently, nice Brønsted acid-promoted C–C bond formation between tetrahydroisoquinolines and *β*-ketoaldehydes or 4-nitrobutyraldehydes was disclosed by the same group.[12] THPBs were also synthesized by this strategy using easily enolizable malonate aldehydes (Figure 1, eq 2).[13] Coupling of 2-methylarylaldehydes with tetrahydroisoquinolines offers a direct approach to the THBP scaffold. However, the construction of a C–C bond from the methyl group of 2-methylbenzaldehyde and a tetrahydroisoquinoline remains elusive because of the poor nucleophilicity of the methyl group.

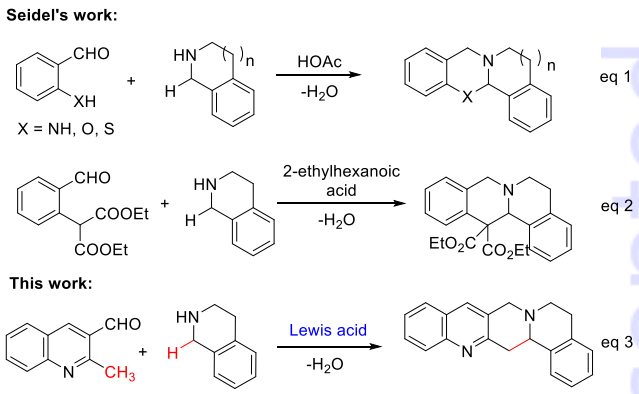

Figure 1. C(sp^3)-C(sp^3) bond formation.

2-Alkylazaarenes, which have similar structures to toluene, have been successfully activated using Lewis acids, such as Pd,[14] Cu,[15] Fe,[16] Sc,[17] Co,[18] Yb[19] and Rh,[20] or Brønsted acids[21] in nucleophilic additions to the C(sp^2) of π-electrophiles. However, Lewis acid-catalyzed C(sp^3)–C(sp^3) bond formation from the corresponding C(sp^3) of 2-alkylazaarenes is unknown. We recently developed a strategy for the activation of inert alkyl and alkenyl groups of aromatics by engineering electron-withdrawing groups into azaarenes. Conjugation addition of aldehydes with amine catalysts to vinylazaarenes,[22] aza–Morita–Baylis–Hillman cascade reactions of

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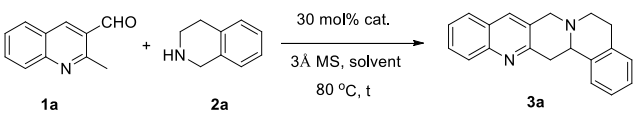
Table 1. Optimization of reaction conditions for annulation reaction.[a)]



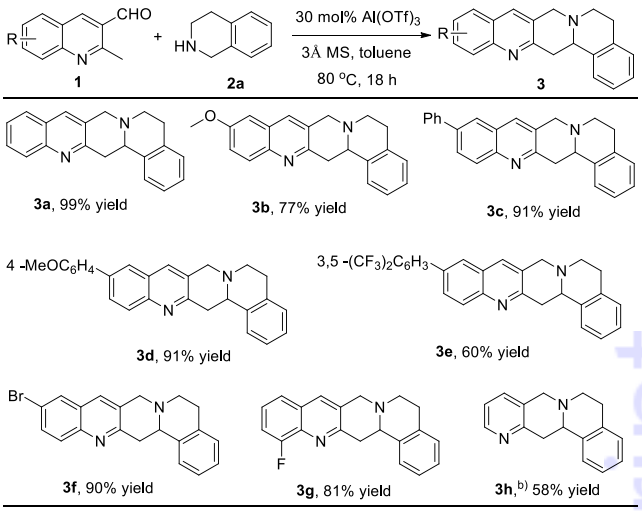
Entry	Catalyst	Solvent	t	Yield (%)[b)]
1[c)]	$Pd(OAc)_2$	toluene	24 h	-
2[c)]	$Cu(OAc)_2$	toluene	24 h	-
3[c)]	$FeCl_3$	toluene	24 h	-
4[c)]	$La(OTf)_3$	toluene	24 h	53
5[c)]	$Sc(OTf)_3$	toluene	24 h	41
6[c)]	$Mg(OTf)_2$	toluene	24 h	54
7[c)]	$Al(OTf)_3$	toluene	24 h	81
8[c, d)]	$Al(OTf)_3$	toluene	24 h	20
9[e)]	$Al(OTf)_3$	toluene	5 d	50
10	$Al(OTf)_3$	toluene	18 h	99
11[f)]	$Al(OTf)_3$	toluene	18 h	60
12[g)]	$Al(OTf)_3$	toluene	18 h	62
13	$Al(OTf)_3$	MeCN	18 h	83
14	$Al(OTf)_3$	EtOH	18 h	30
15	$Al(OTf)_3$	DMF	18 h	39
16	HOAc	toluene	18 h	trace
17	H_3PO_4	toluene	18 h	36
18	HOTf	toluene	18 h	63
19[h)]	HOTf	toluene	18 h	79

[a)] Unless specified, a mixture of **1a** (0.1 mmol) and cat. (30 mol %) was stirred in toluene (1.5 mL) for 30 min at rt. Then 3Å MS (50 mg), **2a** (0.13 mmol) was added before the reaction was carried out at 80 °C. [b)] Isolated yields. [c)] The reaction mixture was stirred at 60 °C. [d)] The reaction mixture was stirred without adding MS. [e)] The reaction mixture was stirred at 40 °C. [f)] 20 mol % $Al(OTf)_3$ was used. [g)] **2a** (0.11 mmol) was used. [h)] 90 mol% HOTf was used.

vinylpyridines[23] and [3+2] cycloaddition of alkylazaarenes to chalcones have been realized.[24] In our continuting efforts on this chemistry, we envisioned that a $C(sp^3)$–$C(sp^3)$ bond could be constructed via Lewis acid-catalyzed intermolecular reactions between 2-methyl-3-carbaldehyde azaarenes and tetrahydroisoquinoline. The tetrahydro-5*H*-isoquinolino[2,1-*g*][1,6]naphthyridine skeleton, which has a very similar core structure to those of THPBs, could therefore be formed in a one-pot cascade annulation reaction (Figure 1, eq 3). Herein, we report an efficient Lewis acid-catalyzed $C(sp^3)$–$C(sp^3)$ bond formation strategy for the synthesis of tetrahydro-5*H*-isoquinolino[2,1-*g*][1,6]naphthyridine derivatives from 2-methylquinoline-3-carbaldehydes and tetrahydroisoquinolines.

The feasibility of this proposed new reaction was investigated using 2-methylquinoline-3-carbaldehyde (**1a**) and 1,2,3,4-tetrahydroisoquinoline (**2a**) as model substrates (Table 1). The reaction was performed in the presence of 30 mol% $Pd(OAc)_2$, 3 Å molecular sieves (MS) in toluene for 24 h at 60 °C. However, the desired product was not detected (entry 1). Other Lewis acids, such as $Cu(OAc)_2$ and $FeCl_3$, did not give the desired product (entries 2 and 3). However,

Table 2. Scope of 2-methylquinoline-3-carbaldehyde derivatives.[a)]



[a)] Unless otherwise specified, a mixture of **1** (0.1 mmol) and $Al(OTf)_3$ (30 mol%) was stirred in toluene (1.5 mL) for 30 min at rt. Then 3Å MS (50 mg), **2a** (0.13 mmol) was added before the reaction was carried out at 80 °C for 18 h. Isolated yields. [b)] The reaction mixture was stirred for 2 d.

the desired product **3a** was isolated in 53% yield when $La(OTf)_3$ was used as the catalyst (entry 4). Other Lewis acids, i.e., $Sc(OTf)_3$ and $Mg(OTf)_2$, gave similar yields (entries 5 and 6). It was found that the yield increased to 81% with $Al(OTf)_3$ (entry 7). Moreover, MS was very important for this reaction. The reaction yield dropped to 20% in the absence of MS (entry 8). The temperature was also critical for the cyclization reaction. Lowering the reaction temperature to 40 °C sharply decreased the reaction efficiency even when the reaction time was prolonged to 5 d (50%, entry 9). A nearly quantitative yield was obtained within 18 h at 80 °C (entry 10). Use of a lower catalyst loading led to decrease of the reaction yield (60%, entry 11). A decrease in the amount of 1,2,3,4-tetrahydroisoquinoline (**2a**) also led to a steep decline in the yield (62%, entry 12). This cyclization was also sensitive to the reaction medium. MeCN gave a slightly lower yield (83%, entry 13). When EtOH and DMF were used, the reactions were sluggish (30% and 39%, entries 14 and 15). Brønsted acids were also tested as catalysts in this annulation reaction too. A weak acid, i.e., HOAc, gave a trace amount of product (entry 16). The reaction yield was increased to 36% when H_3PO_4 was used (entry 17). A strong Brønsted acid (30 mol% HOTf) afforded the product in 63% yield (entry 18). The reaction yield was further enhanced when more amount of HOTf was used (90 mol%, 79%, entry 19). These results suggest that the acidity and acid counter cations are crucial. HOTf can be generated *in situ* from the reaction of $Al(OTf)_3$ with water produced during the reaction. However, a higher reaction efficiency was obtained with $Al(OTf)_3$ as the catalyst (entry 10 vs 19). These results suggest that Al^{III} plays an

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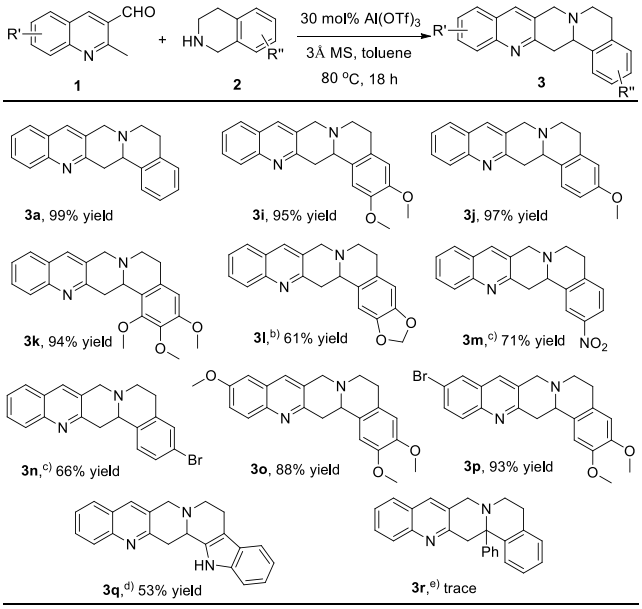
Table 3 Scope of 1,2,3,4-tetrahydroisoquinoline.[a)]

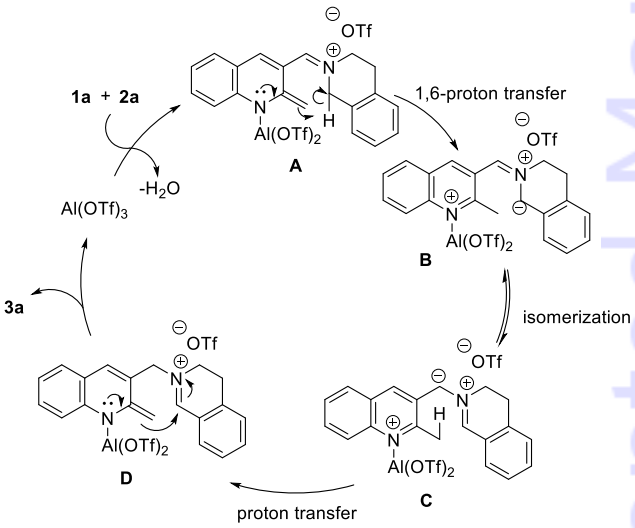


[a)] Unless otherwise specified, a mixture of **1** (0.1 mmol) and $Al(OTf)_3$ (30 mol%) was stirred in toluene (1.5 mL) for 30 min at rt. Then 3Å MS (50 mg), **2** (0.13 mmol) was added before the reaction was carried out at 80 °C for 18 h. Isolated yields. [b)] **2e** (0.05 mmol) was added every 2 d, and the reaction mixture was stirred for 14 d. [c)] The reaction mixture was stirred for 2 d. [d)] The reaction mixture was stirred for 5 d. [e)] The reaction mixture was stirred at 100 °C for 7 d.

important role in facilitating this reaction.

With the optimized reaction conditions in hand, the substrate scope of this cyclization was studied. The data in Table 2 show that a range of substituted 3-aldehyde-2-methylquinolines were tolerated by this annulation reaction. It appears that electronic effect is limited on this process. Electron-donating 6-methoxy group on the phenyl ring of 2-methylquinoline-3-carbaldehyde **1b** delivered the corresponding product **3b** efficiently (77%). 6-Phenyl-3-aldehyde-2-methylquinoline **1c** was also a compatible substrate, giving the annular product **3c** in 91% yield. Similar results were obtained with a 4-methoxylphenyl substituent at the 6-position, giving **3d** (91% yield). The substrate **1e**, which bears a branched 3,5-bis(trifluoromethyl)phenyl group at the C6 position, afforded the product in moderate yield (60%). The electron-withdrawing 6-Br-substituted quinoline **1f** gave **3f** in high yield (90%). In addition, F at the C8 position of 2-methylquinoline-3-carbaldehyde **1g** afforded the desired product **3g** with high efficiency (81%). It should be noted that the less-active substrate 2-methylnicotinaldehyde **1h** could also participate in the process to give the annulation product **3h** (58% yield) after 2 d.

The scope of the 1,2,3,4-tetrahydroisoquinoline component was investigated next (Table 3). The structures carrying electron-donating methoxy groups gave the corresponding products (**3i**–**3k**) in excellent yields (94%-97%) under the standard conditions. Interestingly, the reaction of 6,7-dioxolo substituted 1,2,3,4-tetrahydroisoquinoline **2e** was less efficient (61% yield, **3l**). A seven-fold amount of **2e** and a longer reaction time were needed. Factors other than the electronic characteristics of the substrates also affected the outcomes of the reactions. Substrates with electron-withdrawing groups (7-NO_2 and 6-Br) were all subjected to the standard conditions but requiring much longer reaction times (2 d). But the corresponding products **3m** and **3n** were obtained in good yields (71% and 66%). 3-Aldehyde-2-methylquinoline and 1,2,3,4-tetrahydroisoquinoline with electron-donating groups on the phenyl ring reacted more smoothly to give the corresponding product **3o** (88% yield). An excellent result was obtained from the reaction of 3-aldehyde-2-methylquinoline with an electron-withdrawing group on the phenyl ring and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (93% yield, **3p**). Electron-rich 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole was also tolerated in this reaction, affording the target product **3q** (53%). The cyclization reaction gave only a trace amount of product **3r** even after 5 d when sterically hindered 1-phenyl-1,2,3,4-tetrahydroisoquinoline was used. A similar trend was observed with 2-ethylquinoline-3-carbaldehyde.



Scheme 1. Proposed mechanism for the cyclization reaction.

A reaction cycle for this Lewis acid-catalyzed cyclization is proposed based on a redox-neutral mechanism (Scheme 1).[13] Firstly, an aminal is formed between 3-aldehyde-2-methylquinoline **1a** and 1,2,3,4-tetrahydroisoquinoline **2a**, followed by the Lewis acid activation to produce the zwitterionic intermediate **A**. Then, a key 1,6-proton transfer occurs to form the azomethine ylide intermediate **B**, which isomerizes to intermediate **C**. Because of the adjacent π-system, the second proton transfer occurs, giving the key dipolar complex **D**. Finally, the resulting intermediate **D** undergoes nucleophilic addition to yield the desired annulation product **3a** and releases the Lewis acid.

In summary, we have developed an efficient Lewis acid-catalyzed cyclization for the synthesis of tetrahydro-5*H*-isoquinolino[2,1-*g*][1,6]naphthyridine

derivatives. This method offers a approach to C(sp^3)–C(sp^3) bond conncetion from ainert methyl group through a redox-neutral mechanism. A wide range of substituted 2-methylquinoline-3-carbaldehydes and 1,2,3,4-tetrahydroisoquinolines can be applied for this reaction with good to excellent yields (up to 99%). The annulation products, which have similar structures to those of natural THPBs, can be used for biological studies. Further exploration of this method for new organic transformations and the use of this methodology in the synthesis of biologically relevant molecules are under investigation in our laboratories.

Experimental Section

General Procedure for the Synthesis of Compounds 3

A mixture of **1a** (0.1 mmol) and $Al(OTf)_3$ (0.03 mmol) was stirred in the toluene (1.5 mL) for 30 min under N_2 at room temperature. Then 3 Å MS (50 mg) and a secondary amine **2a** (0.13 mmol) were added. The mixture was stirred at 80 °C. After the reaction was completed (monitored using TLC), the mixture was cooled to room temperature and filtered, the residue was washed with DCM. The combined organic phases were combined and the solvent was evaporated. The residue was purified by column chromatography (neutral alumina) to give the corresponding product **3a**.

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