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Indium-catalyzed C(sp^3)–H functionalization of 2-methylazaarenes through direct benzylic addition to trifluoromethyl ketones†

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The application of trivalent indium for the Lewis acid-catalyzed C(sp^3)–H functionalization of 2-methylazaarenes is reported. InCl$_3$ was discovered to catalyze the direct addition of the benzylic C–H bond in the azaarenes to trifluoromethyl ketones. An ample number of substrates were cogently demonstrated to give the products as tri-fluoromethylated alcohols whereby in some cases, up to quantitative yield (99%) could be obtained.

A substantial degree of advancement has been achieved using indium metal and its salts in organic syntheses.[1] Among the plethora of applications, catalytic protocols based on the inexpensive, low toxic and high tolerance trivalent indium represent an important development in indium chemistry. This had contributed significantly to the establishment of the indium salts as efficient catalysts for carrying out various organic transformations under mild Lewis acid catalysis.[2]

Interest in Lewis acid catalysis has experienced a renaissance as synthetic organic chemists started to adapt to contemporary approaches for transformations leading to the construction of complex organic molecules through C–H functionalization.[3] The azaarenes are among an important class of organic molecules whose synthesis have been described based on the concept of C–H functionalization.[4] In recent developments relating to metal-catalyzed C–H functionalization,[5] several metal salts, largely based upon the transition and rare metals, were utilized in catalytic methodologies for the direct functionalization of benzylic C–H bonds in alkylazaarenes.[6] However, catalytic protocols using salts of the main group metal indium for this class of C–H functionalization remains elusive despite the emergence in the Lewis acid catalysis domain of indium chemistry.[7]

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Therefore, we were consequently motivated to channel our endeavor towards a report on indium-catalyzed C(sp^3)–H functionalization through the direct benzylic addition under Lewis acid catalysis. Specifically, we were interested in the addition of benzylic C–H bond in 2-methylazaarenes to the carbonyl carbons of trifluoromethyl ketones (TFMKs) which are widely regarded as important precursors for the preparation of trifluoromethyl-containing compounds.[8] This approach is effusively welcomed given the astonishing properties of such fluorinated compounds either as pharmaceuticals, agrochemicals or functional materials.[9] Furthermore, susceptibility of TFMKs towards the benzylic C–H additions had only been recently reported.[10] With limited demonstrations conducted in the presence of excess methylazaarenes at a temperature of up to 110 °C, the lanthanide salt Yb(OTf)$_3$ was reported as a suitable Lewis acid catalyst for the addition reaction.

Inevitably, with our ongoing interests in the development of simple and mild methodologies for organic syntheses, the direct addition of C(sp^3)–H bond in 2-methylquinoline (**1a**) to 2,2,2-trifluoro-1-phenylethanone (**2a**) was subsequently initiated. An initial trial under a mild condition consisting of 10 mol% InCl$_3$ in THF at 60 °C gave us an early boost whereby a 93% yield of **3aa** was isolated after 24 h (Table 1, entry 1).

This observation concomitantly led us to justify the role of Lewis acid catalyst in which a set of screening experiments involving several other metal salts was conducted. With InBr$_3$, In(CF$_3$CO$_2$)$_3$, In(OTf)$_3$ and Yb(OTf)$_3$, similar yields of within the probable experimental error corresponding to **3aa** were obtained (entries 2–5). However, results with the chlorides salts of several transition metals are widely diverse. While comparable yields of 92% and 90% were obtainable with CoCl$_2$ and FeCl$_3$ (entries 6 and 7), only 67% and 73% yields of **3aa** were afforded from the reactions performed in the presence of catalytic CuCl$_2$ and MnCl$_2$ (entries 8 and 9). Moreover, the reaction significantly failed to proceed when either NiCl$_2$ or PdCl$_2$ was added to the reaction mixture (entries 10 and 11). The same observation was also made when the reaction was performed under metal-free conditions (entry 12).

Table 1 Optimization studies[a]

Entry	[M]	Solvent	Yield[b] (%)
1	InCl$_3$	THF	93
2	InBr$_3$	THF	91
3	In(CF$_3$CO$_2$)$_3$	THF	90
4	In(OTf)$_3$	THF	95
5	Yb(OTf)$_3$	THF	92
6	CoCl$_2$	THF	92
7	FeCl$_3$	THF	90
8	CuCl$_2$	THF	67
9	MnCl$_2$	THF	73
10	NiCl$_2$	THF	Trace
11	PdCl$_2$	THF	Trace
12	—	THF	Trace
13	InCl$_3$	H$_2$O	94
14	InCl$_3$	^{t}BuOH	99
15	InCl$_3$	^{t}BuOH	99[c]
16	InCl$_3$	^{t}BuOH	99[d]

[a] General reaction conditions: **1a** (2.5 equiv.), **2a** (0.5 mmol), [M] (10 mol%), solvent (0.5 mL), 60 °C, 24 h. [b] Isolated yield. [c] **1a** (1.5 equiv.). [d] **1a** (1.5 equiv.), InCl$_3$ (5.0 mol%).

Satisfied with the importance of Lewis acid catalyst for the reaction, further optimization studies were next contemplated. With our focus firmly set in capitalizing the advantages of indium catalysis, InCl$_3$ was undoubtedly selected due to its practicalities as a Lewis acid catalyst.[11] Water-stability is among the attractive features of InCl$_3$ of which we were keen to exploit due to the array of advantages associated with performing chemical reactions in an aqueous medium.[12] With 94% yield of **3aa** (entry 13), formation of the C–H addition product under the In-catalyzed system is deemed insensitive to the presence of water. However, on the basis of compromising the reaction stoichiometry, ^{t}BuOH was delightfully found to be the best solvent whereby a quantitative yield of **3aa** was achievable (entry 14). Efficiency of the reaction in ^{t}BuOH was also unaffected as we sequentially lowered the excess of **1a** and InCl$_3$ loading. The standard reaction conditions were ultimately established with a catalyst loading of as low as 5 mol% for the quantitative conversion of **2a** to **3aa** in the presence of a slight excess (1.5 equivalent) of **1a** (entry 16).

We next challenged the In-catalyzed protocol for the reactions involving **1a** with various TFMKs. Under the standard reaction conditions, excellent yielding attribute of the protocol was maintained with our demonstrations using bromo-, chloro- and fluoro-substituted 2,2,2-trifluoro-1-phenylethanones (Table 2, entries 1–3). An excellent yield of 98% was also achieved corresponding to product **3ae** which was prepared from trifluoromethyl-substituted TFMK **2e**.

Impressed by the observed reactivity, we next decided to subject our In-catalyzed protocol under stern tests with

Table 2 Scope of TFMKs[a]

Entry	R	Product	Yield[b] (%)
1	Br—C$_6$H$_4$— **2b**	**3ab**	99
2	Cl—C$_6$H$_4$— **2c**	**3ac**	99
3	F—C$_6$H$_4$— **2d**	**3ad**	98
4	F$_3$C—C$_6$H$_4$— **2e**	**3ae**	98
5	**2f**, R^1 = NMe$_2$, R^2 = H; **2g**, R^1 = R^2 = OMe	**3af** **3ag**	N.R.[c]
6	**2h**	**3ah**	90
7	**2i**	**3ai**	36/65[d]
8	**2j**	**3aj**	85
9	**2k**	**3ak**	85
10	**2l**	**3al**	73
11	**2m**	**3am**	46
12	**2n**	**3an**	34[d]
13	**2o**	**3ao**	56
14	**2p**	**3ap**	88

[a] General reaction conditions: **1a** (1.5 equiv.), **2b**–**2p** (0.5 mmol), InCl$_3$ (5.0 mol%) ^{t}BuOH (0.5 mL), 60 °C, 24 h. [b] Isolated yield. [c] N.R. = no reaction. [d] Reaction conducted with 10 mol% InCl$_3$ at 120 °C.

attempts using **2f** and **2g**. However, under the mildness of our standard reaction conditions, the corresponding addition products as **3af** and **3ag** were disappointingly not formed. In these cases, the electron donating as well as steric natures of the

substituents in **2f** and **2g** proved to be too severe in diminishing the electrophilicity of the carbonyl carbons to effect the catalytic addition of C(sp^3)–H bond of **1a**. Further studies aimed at improving the reactivity of the indium-catalyzed protocol for this class of reactions are ongoing in our laboratory.

Nonetheless, to further investigate the scope of TFMKs in our current studies, we next attempted the reaction between **1a** and **2h** which sumptuously resulted in the isolation of **3ah** in 90% yield (entry 6). The successful demonstration with the thiophene-containing TFMK is an indication on the compatibility of heteroaromatic substrates for this class of reaction.

Though lower in reactivity under the standard reaction conditions, **2i** was also found to be a suitable TFMK substrate when the reaction was conducted with 10 mol% InCl$_3$ at 120 °C for the exclusive synthesis of **3ai** as the intended 1,2-addition product in a satisfactory yield of 65% (entry 7).

With **2j** and **2k**, both **3aj** and **3ak** were isolated in 85% yields (entries 8 and 9). No products resulting from 1,4-addition to the α,β-unsaturated alkene moiety were observed despite the excellent Michael acceptor nature of both TFMKs.[13]

Besides selectivity of the C–H addition, the reaction scope was also probed with respect to aliphatic TFMKs during which the Lewis acidity of InCl$_3$ was found to be generally sufficient in catalyzing formation of the intended products. However, addition of the benzylic C–H bond was found to be highly sensitive to the steric environment presented by the hydrocarbons in the vicinity of the carbonyl functionality of these TFMKs. This is evident with **2n** where only 34% of **3an** was isolated despite the influence of an increased catalyst loading and reaction temperature (entry 12).

Ester-functionalized substrates in the form of trifluoroacetoacetate (**2o**) and trifluoropyruvate (**2p**) were also attempted. These led to the isolation of **3ao** and **3ap** in 56% and 88% yields respectively (entries 13 and 14). However, with other types of ketone substrates such as acetophenone and benzophenone, no addition to the ketonic carbon was observed. The inability of these substrates to participate in the reactions indicates the importance of trifluoro moiety for the successful addition of the benzylic C–H bond to the carbonyl carbon.

Scope of 2-methylazaarenes was also explored as we sought to further examine the generality of the current In-catalyzed direct benzylic C–H addition (Table 3).

A series of halogenated substrates was screened for their reactivity in the reaction with **2a**. Notably, chlorine-substituted azaarenes was found to be highly general in their applicability for this addition reaction. This is proven by yields of the addition products being consistently obtained in the excellent range (91–98%) from the azaarenes with chlorine substituent at several different positions on the 2-methylazaarene core (**3ca**, **3da**, **3ea**). However, with 6-fluoro substituent, only a good yield of 75% for **3fa** was afforded as compared to the excellent 94% yield of **3ga** obtained from 7-fluoro-2-methylquinoline. Incorporations of weakly and strongly electron donating groups at the 6-position also exhibited contrasting results with the respective 95% and 58% yields of **3ha** and **3ia**.

Apart from the efficient transformation of 1-methylisoquinoline to **3ja**, substrates with the pyridine core were also

Table 3   Scope of 2-methylazaarenes[a]
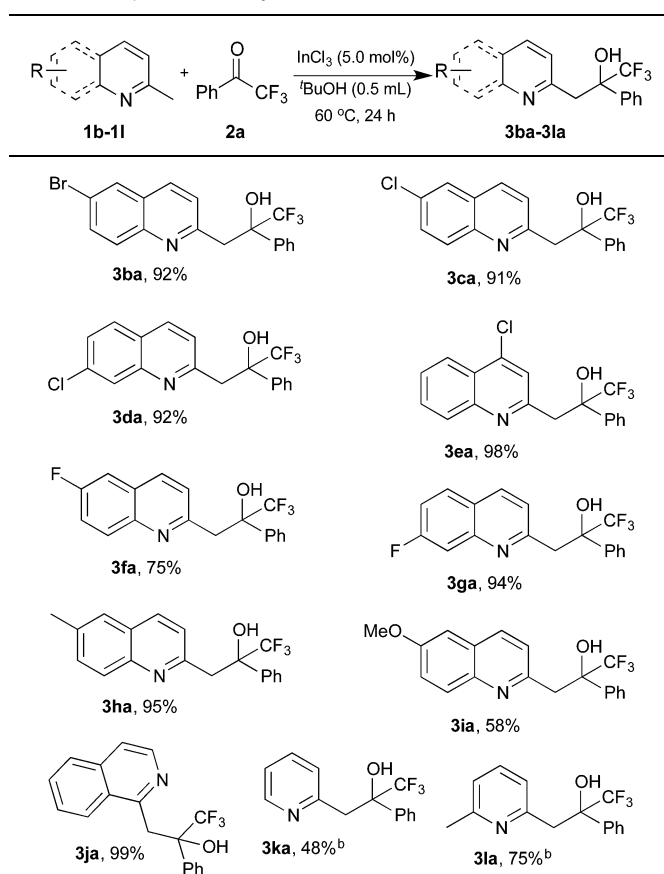
[a] General reaction conditions: **1b–1l** (1.5 equiv.), **2a** (0.5 mmol), InCl$_3$ (5.0 mol%) ^{t}BuOH (0.5 mL), 60 °C, 24 h. [b] Reaction conducted with 10 mol% InCl$_3$ at 120 °C.

tested. Without further optimization of the reaction conditions beyond the utilization of 10 mol% InCl$_3$ at 120 °C, both 2-picoline and 2,6-lutidine were found to participate in the reaction giving **3ka** and **3la** in 48% and 75% yields respectively.

Attempts with other methylheteroaryls such as 3-methylisoquinoline, 4-methylquinoline, 2-methylquinoxaline, 2-methylbenzo[d]oxazole, 2-methylbenzo[d]thiazole and 2-methylthiophene were also conducted. However, no addition products were observed under either the standard or modified reaction conditions.

As a means for understanding the role of In catalyst in our current studies, the deuterium exchange experiments involving 2-methylquinoline (**1a**) in D$_2$O were subsequently conducted. Under the influence of catalytic InCl$_3$ at 60 °C, a marked deuterium incorporation of 27% was observable as compared to result of a control experiment without InCl$_3$ loading (Fig. 1).

A plausible reaction mechanism was then proposed as depicted in Fig. 2.

It is believed that feasibility of the transformations described in this manuscript involves the acidity enhancement of the benzylic C–H bonds by action of the indium catalyst at the Lewis basic site of 2-methylazaarenes. This is brought about by
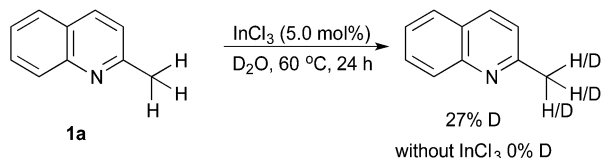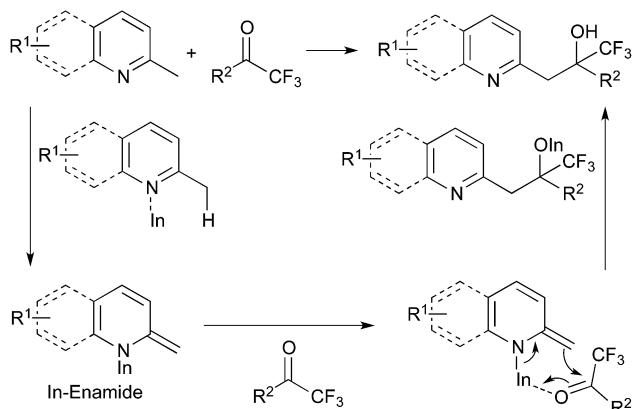
Fig. 1 Deuterium exchange experiments.

Fig. 2 Proposed reaction mechanism.

coordination of the indium Lewis acid to the N atom on the substrates which effectively activates the $C(sp^3)$–H bonds towards their cleavage. This subsequently leads to the formation of indium-enamide intermediates from which addition to the carbonyl carbons of TFMKs proceed to give the intended products.

In conclusion, a simple In-catalyzed $C(sp^3)$–H functionalization through direct benzylic addition under Lewis acid catalysis was successfully developed. InCl$_3$ was found to catalytically promote the addition of benzylic C–H bonds in 2-methylazaarenes to the carbonyl carbons of TFMKs. This protocol is highly efficient in which products of up to quantitative yield could be obtained under mild conditions. In addition to the asymmetric variants, endeavors are also currently directed towards the development of In-catalyzed $C(sp^3)$–H functionalization with other classes of alkylazaarenes and electrophilic acceptors for the C–H addition.

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