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Indium trichloride catalyzed sp^3 C–H bond functionalization of 2-alkyl azaarenes under microwave irradiation

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ABSTRACT

Microwave promoted indium trichloride (10 mol %) catalyzed sp^3 C–H bond functionalization of 2-alkyl azaarenes **1** or **4** has been observed to construct C–C bond either with but-2-ene-1,4-diones **2** or (*E*)-3-(2-oxo-2-phenylethylidene)indolin-2-one (**6**) giving access to 2-((quinolin-2-yl)methyl)butane-1,4-diones **3**, 2-((pyridin-2-yl)methyl)butane-1,4-diones **5**, or 3-(quinolin-2-yl)propan-2-yl)indolin-2-ones **7** in good yields using 1,4-dioxane as solvent.

Direct functionalization of sp^3 C–H bonds to undergo carbon–carbon bond formation attracts considerable attention in modern organic synthesis due to simplicity of overall process.[1] Benzylic sp^3 C–H bond functionalization of 2-alkyl azaarenes such as 2-alkyl quinoline is a challenging task due to inherent nature of less reactivity of alkyl groups. Alkyl azaarene derivatives are known to possess a wide range of pharmacological activities, such as anti-tuberculosis,[2a] anti cancer,[2b–d] anti-inflammatory,[2e] and anti-HIV.[2e] They are also being used as self-organization and complex matter in supramolecular chemistry.[2f,g] Microwave promoted organic transformation has already been established as a reliable tool for getting higher yields of the products under milder reaction conditions and shorter reaction times.[3] In recent time, sp^3 C–H bond functionalization of 2-alkyl substituted azaarene catalyzed by transition metal catalysts,[4] Lewis acids,[5] or Brønsted acids[6] has been reported. Many of these methods are associated with various drawbacks such as use of tedious experimental procedures, unsatisfactory yields, long reaction times, and limited substrate scope. Hence, it has become necessary to develop mild and efficient method and reagent to activate sp^3 C–H bond of 2-methyl azaarene for further generation of C–C bond with suitable substrates. Although, indium belongs to the same group in the periodic table as boron and aluminum, indium salts have become popular among the synthetic organic chemists due to its capability to ensure chemo- and regio-selectivity in various chemical transformations such as Diels–Alder,[7a] aldol,[7b] Friedel–Crafts,[7c] and various other reactions.[8] It is generally considered to be nontoxic to nature, recyclable, and moisture tolerant.[9] As part of our ongoing research program to explore the application of indium chloride for the synthesis of various biologically active heterocyclic compounds,[10] we are delighted to observe that $InCl_3$ under MW irradiation (120 °C, 75 W) could functionalize sp^3 C–H bond of 2-methyl azaarenes, which underwent Michael addition with enedione or indoline-2-one affording alkyl azaarenyl substituted dicarbonyl derivatives in good yields.

Our initial efforts focused on reacting 2-methyl quinoline (**1a**) and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**2a**) in the presence of 10 mol % of $InCl_3$ as a Lewis acid catalyst in THF under conventional heating at 120 °C which afforded 65% of adduct 1,4-diphenyl-2-((quinolin-2-yl)methyl)butane-1,4-dione (**3aa**), whereas, conducting the same reaction under microwave (120 °C, 75 W) in the presence of $InCl_3$, afforded **3aa** in 78% isolated yield (Table 1, entry 1). Hence it has become necessary to optimize the suitable reaction conditions for an easy access to a large number of synthesized products. To investigate the role of solvent and Lewis acid as well as Brønsted acid catalyst in the reaction, various solvents such as THF, 1,4-dioxane, CH_3CN, and toluene, Lewis acid catalysts such as $In(OTf)_3$, $InCl_3$, $ZnCl_2$, and $FeCl_3$, and Brønsted acid catalysts such as acetic acid and TFA were screened (Table 1, entries 1–15). The study revealed that 1,4-dioxane was the suitable solvent of choice and $InCl_3$ was found to be the best among the various catalysts used

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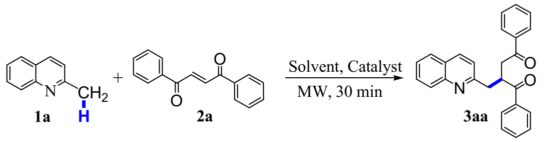
Table 1

Optimization of the reaction conditions[a]



Entry	Solvent	Catalyst (10 mol %)	Yield[b] (%)
1	THF	InCl_3	78
2	Dioxane	In(OTf)_3	44
3	Dioxane	InCl_3	87
4	Dioxane	InBr_3	83
5	Dioxane	In(OAc)_3	58
6	CH_3CN	InCl_3	49
7	^{i}PrOH	InCl_3	73
8	DMF	InCl_3	35
9	DCE	InCl_3	52
10	Toluene	InCl_3	55
11	Dioxane	FeCl_3	53
12	Dioxane	RuCl_3	47
13	Dioxane	ZnCl_2	59
14	Dioxane: water (9:1)	AcOH	61
15	Dioxane: water (9:1)	TFA	66

[a] Reaction conditions: 0.75 mmol of 2-methyl quinoline, 0.5 mmol of (*E*)-1,4-diphenylbut-2-ene-1,4-dione, 1 mL of solvent, MW (120 °C, 75 W), 30 min.

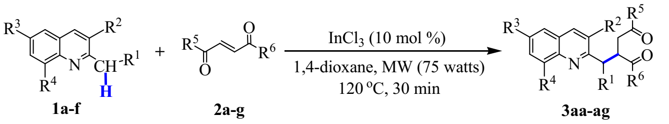
[b] Isolated yields.

(Table 1, entry 3) that afforded the desired product **3aa** in much improved yield (87%) under microwave heating at 120 °C (75 W). Increasing the catalyst loading to 20 mol % did not improve the product yield.

Hence, the ideal reaction conditions under MW irradiation (75 W, 120 °C) were found to be 10 mol % InCl_3 as catalyst and 1,4-dioxane as solvent.[11] Using the optimized reaction conditions, the substrate scope of this reaction was investigated on a series of symmetrical as well as unsymmetrical enediones and the results are summarized in Table 2. Various substituents' effects on azaarenes were also investigated. It seems that there is a correlation between the efficiency of reaction and electronic effect of substituents, since the presence of EWG in azaarene ring afforded slightly higher yield (91%, e.g., NO_2, Table 2, entry 3) in comparison to EDG (e.g., Cl, OCH_3, CH_3; Table 2, entry 2, 4, and 5). Similarly, when 2-ethyl quinoline (**1f**) was used as reactant instead of 2-methyl quinoline (**1a**) it resulted in the expected ethyl azaarenyl substituted dicarbonyl derivative **3fa** as diastereomeric mixture (Table 2, entry 6). Other bulky substituent like 2-cyclohexyl quinoline (**1g**) also underwent C–H functionalization with (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**2a**) to yield the desired product 1,4-diphenyl-2-(1-(quinolin-2-yl)cyclohexyl)-butane-1,4-dione (**3ga**) in 42% yield upon microwave irradiation at 140 °C (100 W) for 30 min (Scheme 1) (see: Supporting information for microwave irradiation profile). Prolonging the reaction time did not improve the yield of **3ga**. It is pertinent to mention that (*E*)-hex-3-ene-2,5-dione (**2g**) did not respond to the reaction, when chosen as coupling partner (Table 2, entry 12). This is probably due to the reduction of the electrophilic character on alkene bond of (*E*)-hex-3-ene-2,5-dione (**2g**) through hyper conjugative effect of two methyl groups which eventually prevents C–C bond formation with 2-methyl azaarenes. Likewise, the electron deficient acetylenes as Michael acceptor did not undergo reaction with azaarenes.

Table 2

Indium trichloride catalyzed sp^3 C–H bond functionalization of 2-alkyl quinolines (**1a–f**) with various enediones (**2a–g**)[a]



Entry	R^1	R^2	R^3	R^4	1	R^5	R^6	2	Product[b]	Yield[c] (%)
1	H	H	H	H	**a**	Ph	Ph	**a**	**3aa**	87
2	H	H	H	Cl	**b**	Ph	Ph	**a**	**3ba**	83
3	H	H	H	NO_2	**c**	Ph	Ph	**a**	**3ca**	91
4	H	H	OCH_3	H	**d**	Ph	Ph	**a**	**3da**	79
5	H	CH_3	H	H	**e**	Ph	Ph	**a**	**3ea**	73
6	CH_3	H	H	H	**f**	Ph	Ph	**a**	**3fa**	78[d]
7	H	H	H	H	**a**	β-np	β-np	**b**	**3ab**	79
8	H	H	H	H	**a**	Ph	OCH_3	**c**	**3ac**	85
9	H	H	H	H	**a**	Ph	CH_3	**d**	**3ad**	72
10	H	H	H	H	**a**	*p*-BrC_6H_4	*p*-BrC_6H_4	**e**	**3ae**	82
11	H	H	H	H	**a**	*p*-MeC_6H_4	*p*-MeC_6H_4	**f**	**3af**	78
12	H	H	H	H	**a**	CH_3	CH_3	**g**	**3ag**	n.r.[e]

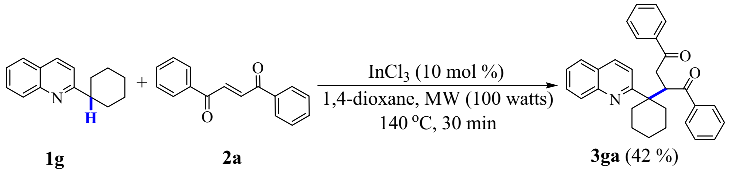
[a] Reaction conditions: 0.75 mmol of 2-methyl quinoline (**1a**), 0.5 mmol of (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**2a**), InCl_3 (10 mol %), 1 mL of 1,4-dioxane, MW (75 W), 120 °C, 30 min.

[b] All products were characterized by NMR, HRMS analysis.

[c] The yields indicated are the isolated yields by column chromatography.

[d] Isolated as inseparable diastereomeric mixture.

[e] No reaction.



Scheme 1. Reaction of 2-cyclohexyl quinoline (**1g**) with *trans*-1,2-dibenzoylethylene (**2a**).