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Ir(III)-catalyzed Regioselective Carbenoid Insertion C−H Alkylation by α-diazotized Meldrum's Acid

Honggui Lv,[†[a,b]] William L. Xu,[†[b]] Kunhua Lin,[[a]] Jingjing Shi*[[b]] and Wei Yi*[[b]]

Abstract: A novel, practical and straightforward protocol via Ir(III)-catalyzed regioselective carbenoid insertion C−H alkylation mediated by α-diazotized Meldrum's acid has been described herein. In no need of the assistance of any external additives and oxidants, the developed Ir(III) catalysis proceeds in a highly efficient manner (*e.g.* mild reaction condition, shorter reaction time and excellent regioselectivity) and demonstrates good compatibility with several privileged substrates, such as valuable *N*-(2-pyrimidyl)indoles, phenylpyridines, and the marketed drug-Edaravone and its analogs, thus providing a *good* complement to previous methods for the rapid construction of their corresponding alkylated products.

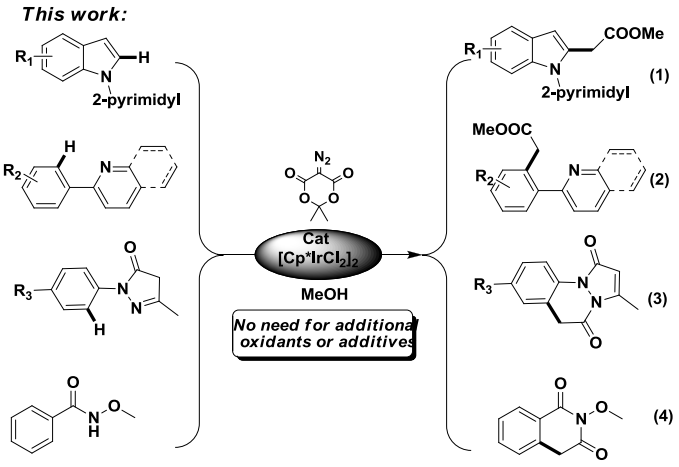
Introduction

The direct regioselective activation of ubiquitous C−H bonds for tandem constructing C−C and/or C−Het bonds has attracted considerable attention in modern synthetic chemistry since it holds great potential in reshaping traditional organic synthesis procedures.[1] As a result, a tremendous number of elegant examples from transition-metal catalyzed and directing group (DG)-assisted direct C−H functionalization have been extensively reported in the past decades. [2,3] Generally, the involvement of an external oxidant is indispensable to the turnover of the catalytic cycle in the C−H activation reactions. However, it also often leads to additional costs and production of unwanted by-products. Therefore, though it is challenging, it is highly desirable to achieve the transition-metal-catalyzed C−H activation for the cascade formation of C−C and/or C−Het bonds without the assistance of any external oxidants.

To address this issue, a versatile approach employing an auto-cleavable oxidazing-substrate precursor (ACOSP) as the coupling partner has been disclosed in recent years. [4,5] Among these developed ACOSPs, diazo compounds play a particularly prominent role[5] due to their intrinsic advantages such as high efficiency, mild reaction conditions, and excellent chemoselectivity. Following the pioneering work of Yu and coworkers, [6] and to date, remarkable progress has been made in the Rh(III)-catalyzed carbenoid insertion C−H functionalization with diazo compounds derived from malonates and β-ketoesters. [7]

Despite these advances, there is room for innovation, both in developing *a* new and *simple* catalyst *system* and in improving the currently limited substrate scope. For example, in the above Rh(III)-catalyzed reactions, the mandatory addition of the additive was usually necessary for the high catalytic efficiency, in spite of avoiding the use of external oxidant. Moreover, in sharp contrast to chain diazo compounds, the cyclic diazo compounds that used as versatile ACOSPs were much less documented in the literature, [8,9] especially in Ir(III)-catalyzed C−H functionalization, for which only two examples have been reported by the groups of Wang[9a] and Ramana. [9b] Nevertheless, the corresponding Ag salt additives were also found to be involved in their developed reactions. Undoubtedly, further development of a *simple and efficient* Ir(III)-catalyzed carbenoid insertion C−H functionalization using cyclic diazo compounds as the ACOSPs, with no need of the assistance of any external oxidants and additives, is still of prime synthetic value and quite needful in view of green and sustainable chemistry.

Inspired by the above information and in combination with the recent breakthroughs in the field of Ir(III)-catalyzed C−H activation, [10] we herein disclose a simple (no need of any external additives and oxidants), efficient (commonly for 2 h), and straightforward (one-pot construction of valuable 2-acetate substituted indole products) Ir(III) catalytic system for regioselective carbenoid insertion C−H alkylation of indoles, which was mediated by α-diazotized Meldrum's acid and MeOH (eqn (1)). The extension of the developed Ir(III) catalytic system to other important substrates, such as classical phenylpyridines (eqn (2)), the marketed drug-Edaravone(eqn (3)) and *N*-methoxybenzamide(eqn (4)) as well, has also been demonstrated successfully for the first time, and thus giving the corresponding alkylated products in a step-economical fashion.



Results and Discussion

At the outset, we examined this Ir(III)-catalyzed and α-diazotized Meldrum's acid-mediated carbenoid insertion reaction in MeOH employing commercially available [Cp*Ir(Cl)$_2$] as the active catalyst, and using *N*-(2-pyrimidyl)-functionalized indole **1a** as the model substrate since it has given a success story in our previous studies. [8d,11] To our delight, the anticipated product **3a** was cleanly generated in 83% isolated yield under the initial

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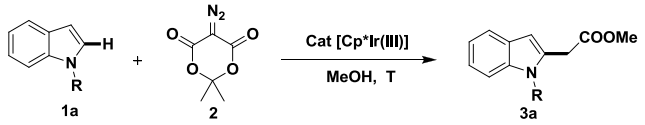
conditions (Table 1, entry 1), in which the inherently reactive C-3 position of the indole core was untouched. Subsequently, an attempt to either increase or decrease the reaction temperature both clearly inhibited the process (entries 2-3), implying that a balance between the reactivity and the substrate decomposition might exist within the reaction. Notably, the introduction of AgOAc and $Ag(SbF_6)_2$ to the current Ir(III) catalyst system did not improve the reaction efficiency (entries 4-5), although previous reports have demonstrated that the Ag salt could activate the transition-metal catalyst in highly efficient manner.[2,9] Gratifyingly, reducing the catalyst loading from 5 mol % to 2.5 mol % led to the isolation of **3a** in an equivalent yield of 81% (entry 6). Finally, the control experiments indicated that no desired product was formed in the absence of catalyst or *N*-(2-pyrimidyl) group (entries 7-8). In summary, the optimal conditions of the carbenoid insertion C−H alkylation were $[Cp^*Ir(Cl)_2]$ (2.5 mol %) at 100 °C in MeOH for 2 h under air.

Table 1 Selected optimization of reaction conditions[a]

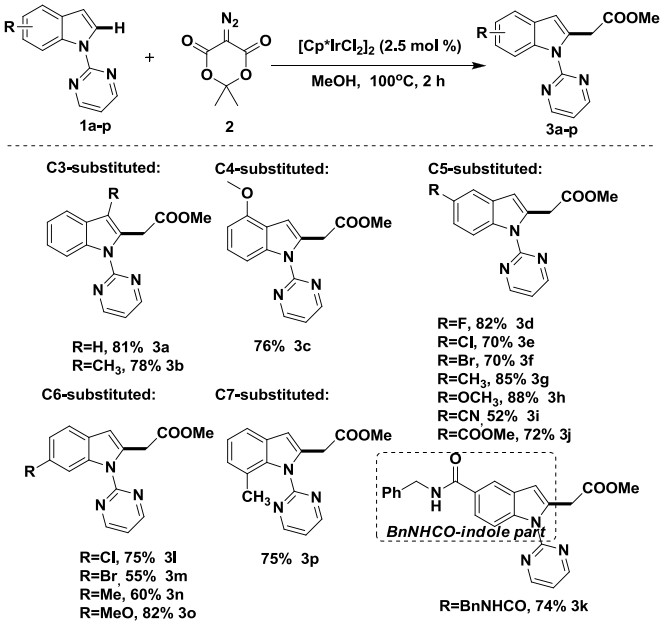


Entry	R	Catalyst system (mol %)	T (°C)	Yield[b] (%)
1	2-Pyrimidyl	$[Cp^*IrCl_2]_2$ (5)	100	83
2	2-Pyrimidyl	$[Cp^*IrCl_2]_2$ (5)	80	67[c]
3	2-Pyrimidyl	$[Cp^*IrCl_2]_2$ (5)	120	71
4	2-Pyrimidyl	$[Cp^*IrCl_2]_2$ (5), AgOAc(20)	100	76
5	2-Pyrimidyl	$[Cp^*IrCl_2]_2$ (5), $AgSbF_6$(20)	100	59
6	**2-Pyrimidyl**	**$[Cp^*IrCl_2]_2$ (2.5)**	**100**	**81**
7	H	$[Cp^*IrCl_2]_2$ (5)	100	0
8	2-Pyrimidyl	----------	100	0
9	2-Pyrimidyl	**$[Cp^*RhCl_2]_2$ (2.5)**	100	73[d]

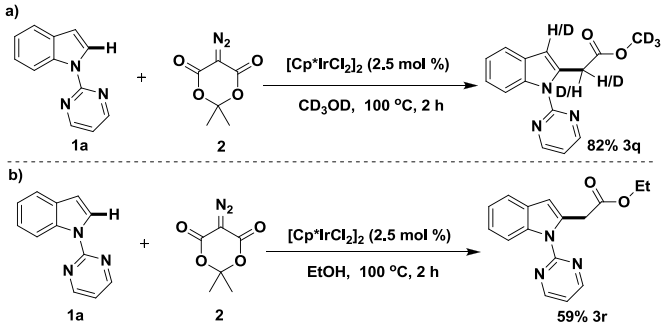
[a] Reaction conditions: **1a** (0.22 mmol, 1.1 eq), **2** (0.2 mmol, 1.0 eq), $[Cp^*IrCl_2]_2$ (X mol %), MeOH (1.0 mL), 2 h, under air. [b] Isolated yields. [c] Reaction for 12 h. [d] Reaction for 24 h, 23% start material **2** was recovered.

With the optimized conditions in hand, we sought to examine the scope of indoles and the generality of this reaction, and the results were given in Scheme 1. In general, the indole substrate bearing the substituent either at the C3- (**1b**), C4- (**1c**), C5- (**1d–k**), C6- (**1l–o**), or C7- (**1p**) position all efficiently coupled with α-diazotized Meldrum's acid **2** in MeOH to give the corresponding C2-ethyl acetate substituted indoles in moderate to good yields (52–88%) and with exclusive regionselectivities, in which both electron-donating and -withdrawing groups were also all well tolerated regardless of the electronic properties of the substituent on the indole skeleton. Moreover, the reaction showed good compatibility with a wide range of valuable functional groups including fluoro (**3d**), chloro (**3e** and **3l**), bromo (**3f** and **3m**), and methoxy (**3h** and **3o**), cyano (**3i**), ester (**3j**) substituents. Notably, indole **1k** with a bulkier BnNHCO substituent was also found to be quite compatible, thus providing the desired product **3k** in 74% yield. Since the BnNHCO-substituted indole part has represented a key structural motif found in many PPARγ modulators,[11a,12] this reaction provides an attractive strategy for the rapid and efficient synthesis of new potential PPARγ modulators for anti-diabetic drug discovery.

After reviewing the aforementioned results, we concluded that MeOH has two key roles both as a solvent and as a reagent in the carbenoid insertion C−H activation reaction. To further confirm this, CD_3OD, instead of MeOH, was subjected to the reaction at first (Scheme 2a). The result demonstrated that it was proceeded smoothly to deliver the methyl-deuterated **3q** in good yield, along with additional deuterium incorporation at the C2-α- and C3-positions of the indole (for detail, see ESI†). Additionally, running the reaction in EtOH also worked well to give the desired product **3r** in a synthetically useful yield (Scheme 2b). Overall, these results not only further corroborated our reasoning but also provided an insight into the reaction mechanism.



Scheme 1 Scope of indoles. Reaction conditions:**1a-p** (0.22 mmol), **2** (0.20 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%), MeOH (1.0 mL), 2 h, under air; yields refer to isolated yields.



Scheme 2 The investigation for the role ofmethanol. Reaction conditions: **1a** (0.22 mmol), **2** (0.20 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), alcohol (1.0 mL), 2 h, under air; yields refer to isolated yields.

We next performed two different experiments to unveil the nature of the reaction mechanism. First, the reversibility of the C–H activation step in the Ir(III) catalytic system was defined by

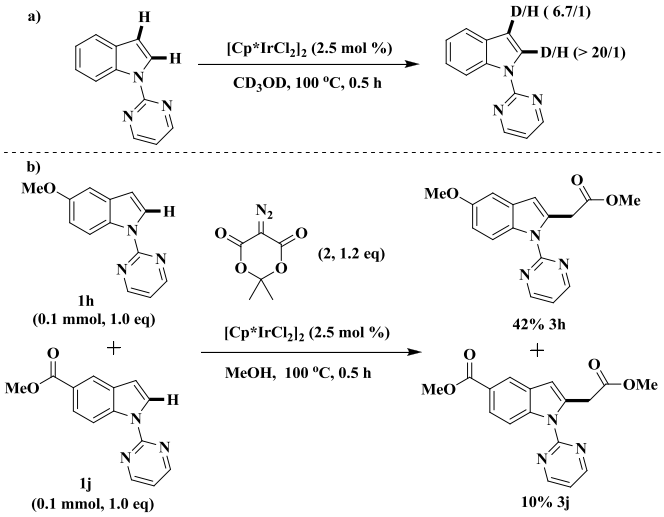
running the reaction in CD_3OD in the absence of α-diazotized Meldrum's acid **2**. As illustrated in Scheme 3a, after stirring the reaction for 0.5 h, a significant deuterium incorporation of **1a** was detected by NMR analysis (for C-2 position, D : H > 20 : 1; for C-3 position, D : H = 6.7 : 1), revealing that the Ir(III)-catalyzed C2–H bond activation process is largely reversible. [13] Subsequently, an intermolecular competition experiment between differently substituted indoles was conducted to delineate the action mode of the reaction (Scheme 3b). To this end, the result revealed electron-rich indoles to be inherently more reactive (*e.g.* **3h**/**3j** = 4.2 : 1), suggesting that they are better substrates than electron-deficient indoles, and also implying that the C–H activation reaction may be via an internal electrophilic substitution (IES)-type mechanism. [14]

Considering the remarkable versatility displayed by the Ir(III) catalytic system, we proceeded to expand its synthetic utility for the carbenoid insertion C−H alkylation of other substrates (Scheme 4). We first selected classical phenylpyridine **4a** and the marketed drug-Edaravone **6a** as the corresponding model substrates for this exploration, as such transformation has not yet been reported in the field of Ir(III)-catalyzed C−H functionalization. As expected, the coupling with **4a** occurred successfully to give the alkylated product in a good yield. Very interestingly, the reaction with Edaravone could also be run smoothly without difficulty, and an alkylation/annulation product **7a** was then obtained in a decent yield and with a faster reaction process (0.5 h vs 2 h) though regioselective carbenoid insertion C–H activation, C-C coupling, and cyclization cascade. [15]

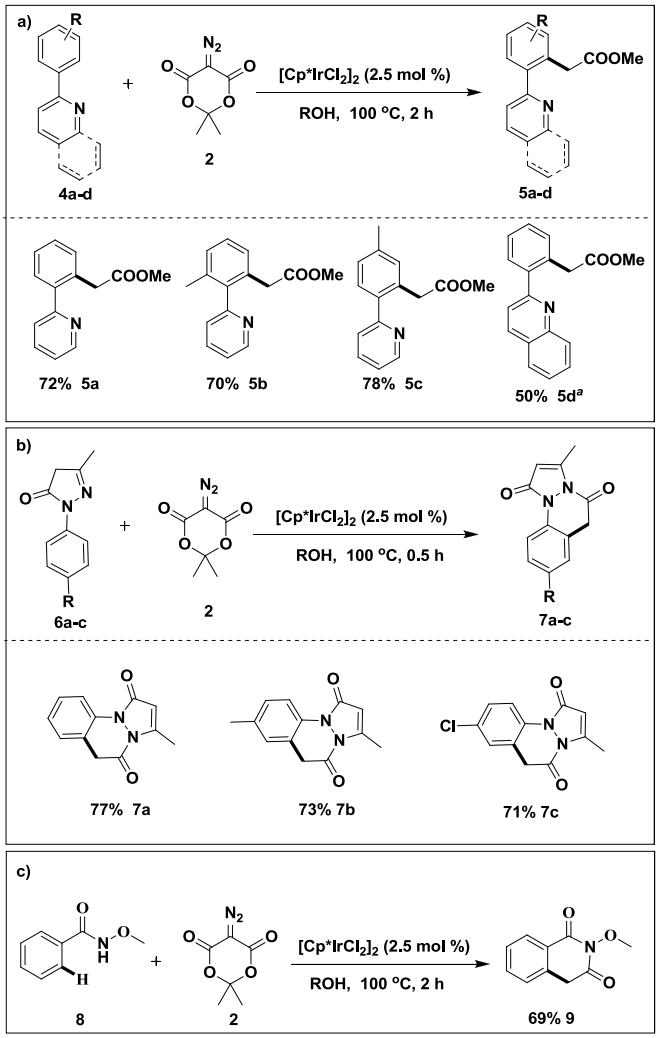
Encouraged by the above results, finally several phenylpyridines (**4a-c**), Edaravone analogs (**6a-c**) and *N*-methoxybenzamide was used to further test the availability of the established Ir(III) catalysis. As shown in Scheme 4, α-diazotized Meldrum's acid coupled efficiently with these selected substrates to deliver the corresponding products **5b-c**, **7b-c** and **9** with excellent regioselectivities and in synthetically useful yields (70-78%). Intriguingly, switching pyridyl to quinolyl also furnished the desired product **5d** in 50% yield. Taken together, these results not only illustrated the remarkable robustness of this Ir(III)-catalyzed system but also provided a highly attractive strategy to construct new analogs of Edaravone for immediate drug screening.

Conclusions

In summary, we have developed the first Ir(III)-catalyzed and carbenoid insertion C−H alkylation of indoles with α-diazotized Meldrum's acid giving direct access to 2-acetate substituted indoles with excellent regioselectivities and functional group tolerance and in moderate to good yields, where only $[Cp^*IrCl_2]_2$ was used as the catalyst system and neither extra additive nor oxidant were required. Further extension of the simple and convenient Ir(III) catalysis to classical phenylpyridine and the marketed drug-Edaravone substrates also produced the satisfactory results. Thus, these versatile reactions presented provide a *good* complement to previous methods for the construction of the corresponding target products. We expect the developed Ir(III) catalytic system to evoke more C–H activation reactions for alternate and step-economical synthesis of other privileged building blocks.



Scheme 3 Mechanistic experiments.



Scheme 4 The investigation for synthetic utility of the Ir(III) catalytic system using phenylpyridines, the marketed drug-Edaravone and its analogs as substrates. Reaction conditions: **4** or **6** or **8** (0.22 mmol), **2** (0.20 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol %), MeOH (1.0 mL), 2 h or 0.5 h, under air. yields refer to isolated yields. [a]Reaction for 8 h.

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental procedures, compound characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgements

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Keywords: Ir(III)-catalyzed • C−H alkylation • indole • α-diazotized Meldrum's Acid

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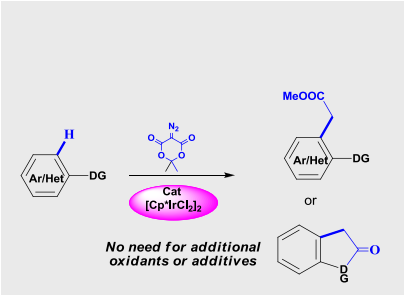
COMMUNICATION

A novel and simple protocol via Ir(III)-catalyzed carbenoid insertion C−H alkylation mediated by α-diazotized Meldrum's acid has been developed.



C−H alkylation

H. Lv, W. L. Xu, K. Lin, J. Shi and W. Yi**

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Ir(III)-catalyzed Regioselective Carbenoid Insertion C−H Alkylation by α-diazotized Meldrum's Acid