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Iron-Catalyzed C(sp^3)–H Functionalization of Methyl Azaarenes: A Green Approach to Azaarene-substituted α- or β-Hydroxy Carboxylic Derivatives and 2-Alkenylazaarenes

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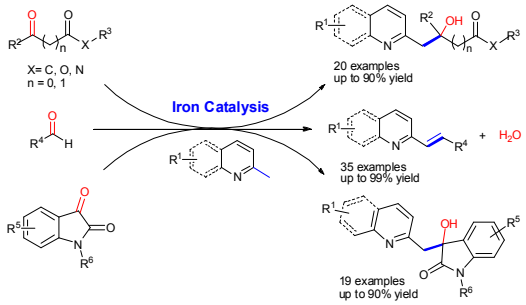

An iron-catalyzed C(sp3)–H functionalization of methyl azaarenes with carbonyls to access the title compounds have been described

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Paper

Iron-Catalyzed C(sp^3)–H Functionalization of Methyl Azaarenes: A Green Approach to Azaarene-substituted *α*- or *β*-Hydroxy Carboxylic Derivatives and 2-Alkenylazaarenes

Danwei Pi,[a,‡] Kun Jiang,[a,‡] Haifeng Zhou,[*a,b] Yuebo Sui,[a] Yasuhiro Uozumi[*a,b], Kun Zou[a]

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Bioactive azaarene-substituted lactic acids, *β*-hydroxy esters, 3-hydroxy-2*H*-indol-2-ones, and 2-alkenylazaarenes were prepared in moderate-to-excellent yields via C(sp^3)–H functionalization of methyl azaarenes with carbonyl compounds in the presence of iron(II) acetate as an inexpensive, nontoxic, efficient catalyst. The application of this atom-, step-economic, and environmentally friendly method was demonstrated by a gram-scale synthesis of 3-[(*E*)-2-(7-chloroquinolin-2-yl)vinyl]benzaldehyde, a key intermediate of leukotriene receptor antagonist (Montelukast).

Introduction

Modern sustainable organic synthesis requires the development of novel, efficient, atom-, and step-economic functional-group transformations.[1] The direct C(sp^3)–H bond functionalization of 2-alkyl azaarenes is such a transformation. Consequently, some efforts have been expended on this type of reactions. Recently, the C(sp^3)–H bond functionalization of 2-alkyl azaarenes catalyzed by palladium,[2] Lewis acids,[3] BrØnsted acids[4] or under catalyst-free conditions,[5] have appeared. For example, Huang and co-workers reported the addition of 2-alkyl azaarenes to the C=N double bonds of *N*-sulfonyl aldimines.[3a-c] Kanai reported the direct addition of alkyl-substituted azaarenes to the C=C double bonds of enones promoted by $Sc(OTf)_3$.[3e] Xiao and Li reported the TfOH-catalyzed addition of 2-methyl pyridines to C=O double bonds of isatins.[4a] Guo and co-workers realized the direct addition of 2-alkyl azaarenes to ethyl azodicarboxylates.[3i] Very recently, the C(sp^3)–H bond functionalization of 2-alkyl azaarenes via oxidative cross dehydrogenative coupling was reported.[6] The derivatives of 2-alkyl azaarenes are biologically important compounds.[7] Although some elegant methods have emerged, the development of mild, high efficient, environmentally friendly, and practical methods for the direct C(sp^3)–H bond functionalization of 2-alkyl azaarenes are still highly desirable.

Azaarene-substituted lactic acid derivatives are potential components of various biologically active compounds. However, very limited methods were available for their preparation.[3f-g,8] The Darzen's condensation of an aromatic aldehyde with ethyl chloroacetate followed by catalytic hydrogenation is a typical approach to access these compounds.[8a] They also can be prepared by the addition of 2-methyl azaarenes to *α*-oxoesters catalyzed by $Yb(OTf)_3$,[3g] or $Cu(OTf)_2$/1,10-phennanthroline.[3f]

3-Substituted-3-hydroxy-2*H*-indol-2-ones are structural moiety of natural products and biologically active compounds (Figure 1).[9] The biological properties of such compounds are affected by the nature of substituents at the C3 position.[9d] Several methods have emerged for the synthesis of aryl- or alkyl-substituted derivatives.[10] However, very few methods were disclosed for preparing 3-azaarene-substituted 3-hydroxy-2*H*-indol-2-ones.[11] For example, these compounds were synthesized by the addition of 2-alkyl azaarenes to isatins in the presence of TfOH,[4a] Iodine,[3k] $Yb(OTf)_3$,[3j] or under catalyst-free conditions[4b, 5b, 5c].

2-alkenylazaarenes are bioactive compounds,[12] as well as the precursors of 2-alkylheterocycles (Figure 1).[13] These compounds were originally synthesized from 2-methylazaarenes and aldehydes promoted by stoichiometric amount of acetic anhydride or aqueous alkali.[14] The Pd-, Ru-, Ni-, and Cu-catalyzed direct alkenylation of activated pyridines or quinolines to give 2-alkenylazaarenes have also been realized.[15] Recently, Huang and co-workers developed an iron-catalyzed synthesis of *trans*-2-alkenylazaarenes through the addition of 2-methyl azaarenes to *N*-sulfonylaldimines, with subsequent C–N bond cleavage.[3c] Wang and co-workers improved the same reaction under catalyst-free condition.[5a]

We have developed a facile approach to prepare azaarene-substituted lactic acid derivatives via iron-catalyzed C(sp^3)-H functionalization of methyl azaarenes with *α*-oxoesters.[16] Here, we reported the systematic study of C(sp^3)–H functionalization of methyl azaarenes with carbonyl or dicarbonyl compounds in the presence of iron(II) acetate. The practical potential of this method was demonstrated by a gram-scale synthesis of 3-[(*E*)-2-(7-chloroquinolin-2-yl)vinyl]benzaldehyde, a key intermediate of the leukotriene receptor antagonist (Montelukast).

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† Electronic Supplementary Information (ESI) available: Experimental procedures, compound chracterizations, and copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/b000000x/

‡ These authors contributed equally to this work.

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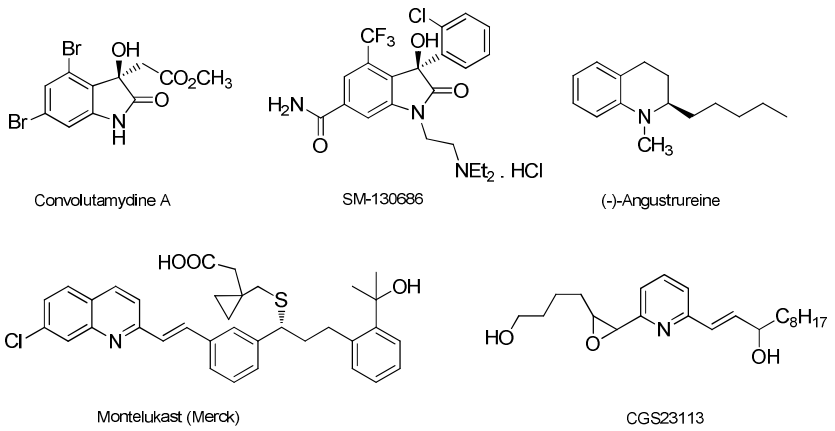


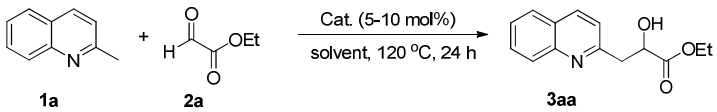
Figure 1. Representative biologically active compounds containing the title structures

Results and Discussion

C(sp^3)–H Functionalization of Methyl Azaarenes with *α*- or *β*-Ketoesters

Initially, the reaction of 2-methyl quinoline **1a** and ethyl glyoxylate **2a** catalyzed by iron (II) acetate in toluene at 120 °C for 24 h was selected as a model reaction. As shown in table 1, the ethyl 2-hydroxy-3-quinolin-2-ylpropanoate **3aa** was obtained in 32% yield (entry 1). A survey of solvents showed that 1,4-dioxane is an optimal candidate comparing to toluene, tetrahydrofuran, methyl *tert*-butyl ether, 1,2-dichloroethane, acetonitrile, *N,N*-dimethyl formide, 1,2-dimethoxyethane (entries 1-8). It was found that the yields of **3aa** varied with the ratios of the two starting materials, an excess amount of ethyl glyoxylate **2a** resulted in low reactivity. In contrast, the yield of **3aa** reached to 89% when an excess amount of 2-methylquinoline **1a** was used (entries 2 and 9–13). The yield of **3aa** remained unchanged with decreased catalyst loading (entry 14), but no reaction occurred in the absence of iron salts (entry 15). Under the identical reaction conditions to those shown in entry 14, other iron salts, such as $FeCl_3$, $Fe(OTf)_2$, $Fe(BF_4)_2.6H_2O$, $Fe(ClO_4)_3.6H_2O$, $Fe(acac)_3$, copper salts $Cu(OAc)_2$, $Cu(OTf)_2$, and $Sc(OTf)_3$ were examined. $Fe(OAc)_2$ was proved to be the most effective catalyst in this transformation (entries 14, 16-23).

Table 1. Optimization of the reaction conditions [a]



1a **2a** **3aa**

Entry	Catalyst (mol%)	**1a** (mmol)	**2a** (mmol)	Solvent	Yield [%][b]
1	$Fe(OAc)_2$ (10)	0.4	0.6	toluene	32
2	$Fe(OAc)_2$ (10)	0.4	0.6	1,4-dioxane	50
3	$Fe(OAc)_2$ (10)	0.4	0.6	THF	48
4	$Fe(OAc)_2$ (10)	0.4	0.6	MTBE	35
5	$Fe(OAc)_2$ (10)	0.4	0.6	$Cl(CH_2)_2Cl$	23
6	$Fe(OAc)_2$ (10)	0.4	0.6	MeCN	32
7	$Fe(OAc)_2$ (10)	0.4	0.6	DMF	10
8	$Fe(OAc)_2$ (10)	0.4	0.6	$MeO(CH_2)_2OMe$	44
9	$Fe(OAc)_2$ (10)	0.4	0.8	1,4-dioxane	31
10	$Fe(OAc)_2$ (10)	0.4	1.0	1,4-dioxane	5
11	$Fe(OAc)_2$ (10)	0.6	0.4	1,4-dioxane	77
12	$Fe(OAc)_2$ (10)	0.8	0.4	1,4-dioxane	85
13	$Fe(OAc)_2$ (10)	1.0	0.4	1,4-dioxane	89
14	$Fe(OAc)_2$ (5)	1.0	0.4	1,4-dioxane	90
15	–	1.0	0.4	1,4-dioxane	nd

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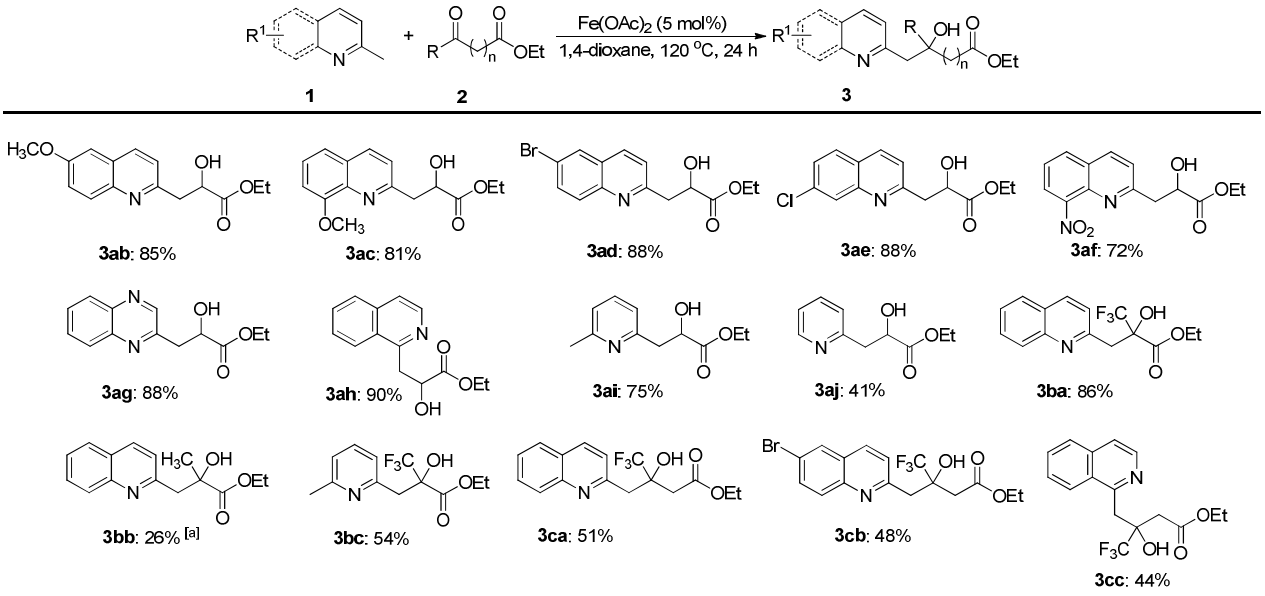
16	$FeCl_3$ (5)	1.0	0.4	1,4-dioxane	22
17	$Fe(OTf)_2$ (5)	1.0	0.4	1,4-dioxane	60
18	$Fe(BF_4)_2.6H_2O$ (5)	1.0	0.4	1,4-dioxane	21
19	$Fe(ClO_4)_3.6H_2O$ (5)	1.0	0.4	1,4-dioxane	37
20	$Fe(acac)_3$ (5)	1.0	0.4	1,4-dioxane	55
21	$Cu(OAc)_2$ (5)	1.0	0.4	1,4-dioxane	57
22	$Cu(OTf)_2$ (5)	1.0	0.4	1,4-dioxane	65
23	$Sc(OTf)_3$ (5)	1.0	0.4	1,4-dioxane	nd

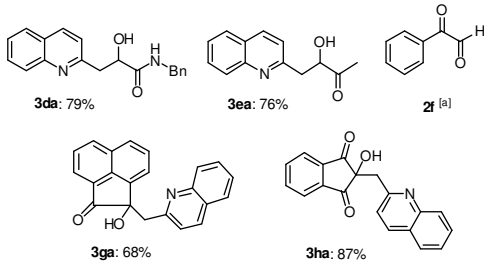
[a] *Reaction conditions*: 2-methylquinoline **1a**, ethyl glyoxylate **2a**, solvent (1 mL), 120 °C, 24 h. [b] Isolated yield. [c] nd = not detected.

Under the optimal conditions, the scope of various methyl azaarenes **1** and *α*- or *β*-ketoesters **2** was investigated. As shown in Scheme 1, the reactions of ethyl glyoxylate **2a** and 2-methyl azaarenes bearing electron-rich or electron-deficient substituents proceeded smoothly to give the azaarene-substituted ethyl lactates **3ab**–**3af** in 72–88% yield. In comparison with electron-rich 2-methylazaarenes, electron-deficient 2-methyl-8-nitroquinoline **1f** gave hydroxy ester **3af** in a relatively low yield of 72%. The reactions of 2-methylquinoxaline **1g** or 1-methylisoquinoline **1h** with **2a** also gave the desired products **3ag** and **3ah** in 88% and 90% yield, respectively. Furthermore, the reactions of **2a** with 2,6-dimethylpyridine **1i** or 2-methylpyridine **1j** also proceeded to give moderate yields of products **3ai** and **3aj**, respectively. Except for ethyl glyoxylate, the ethyl 3,3,3-trifluoropyruvate, ethyl pyruvate were also subjected to this transformation. The reaction of 2-methyl quinoline **1a** and ethyl 3,3,3-trifluoropyruvate proceeded successfully to give the product **3ba** in 86% yield. However, when ethyl pyruvate was used instead of ethyl 3,3,3-trifluoropyruvate, only 26% yield of **3bb** was obtained even if increasing the catalyst loading and temperature. It revealed that the electron-withdrawing group of ketoester **2** enhanced the reactivity of carbonyl. The *β*-ketoester ethyl 4,4,4-trifluoroacetoacetate was also applicable to this reaction, and the products **3ca**–**3cc** were obtained in relatively moderate yield (44-51%).



Scheme 1. Substrate scope of methyl azaarenes and *α*- or *β*-ketoesters. *Reaction conditions*: methylazarene **1** (1.0 mmol), *α*- or *β*-ketoester **2** (0.4 mmol), $Fe(OAc)_2$ (0.02 mmol), 1,4-dioxane (1 mL), 120 °C, 24h, isolated yield. [a] $Fe(OAc)_2$ (10 mol%), 130 °C, 24 h.

Encouraged by the success of the reaction of methyl azaarenes with *α*- or *β*-ketoesters, we extended the carbonyls to other 1,2-dicarbonyl compounds. As shown in Scheme 2, *N*-Benzyl-2-oxoacetamide **2d** and methylglyoxal **2e** were compatible to this transformation, giving the products **3da** and **3ea** in 79% and 76% yield, respectively, whereas phenylglyoxal **2f** decomposed under the reaction conditions. The cyclic diketones acenaphthoquinone **2g** and ninhydrin [**2h**: 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione] were also compatible to this reaction, giving the products **3ga** and **3ha** in 68% and 87% yield, respectively.



Scheme 2. Reactions of **1a** with other 1,2-dicarbonyl compounds. *Reaction conditions:* 2-methyl quinoline **1a** (1.0 mmol), 1,2-dicarbonyl **2** (0.4 mmol), $Fe(OAc)_2$ (10 mol%), 1,4-dioxane (1 mL), 120 °C, 24 h (isolated yield). [a] Decomposed under the reaction conditions.

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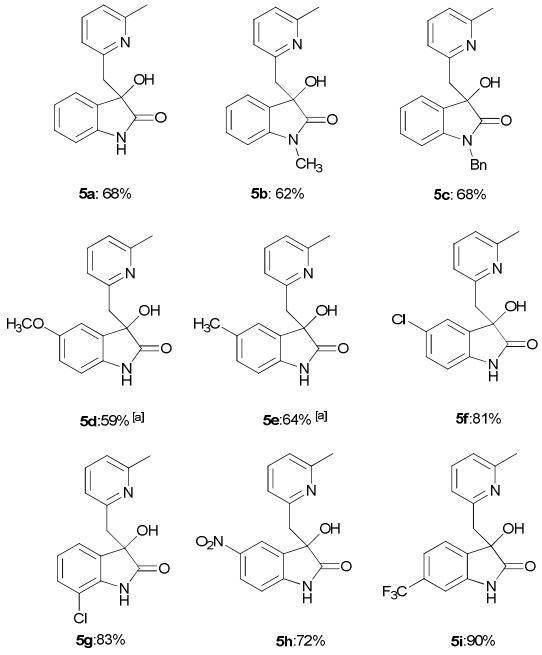
C(sp^3)–H Functionalization of Methyl Azaarenes with Isatins

Although some methods for preparing 3-azaarenylmethyl-3-hydroxy-2-oxindole derivatives from isatins and methyl azaarenes have appeared,[3,5] they suffered from some drawbacks: 1) the reaction partners of isatins were limited to methyl pyridines; 2) the *N*-protected isatins were essential for good yield. Inspired by the success of the reaction of methyl azaarenes with glyoxylate, *α*- or *β*-ketoesters, and 1,2-dicarbonyl compounds, as shown in Scheme 3, we examined the reaction of isatin (**4a**; 1*H*-indole-2,3-dione) with 2,6-dimethylpyridine in the presence of 10 mol% $Fe(OAc)_2$ at 120 °C for 24 h. The desired product **5a** was obtained in 68% yield. To explore the scope of this reaction for the synthesis of 3-azaarene-substituted 3-hydroxy-2*H*-indol-2-ones, we screened the reactions of 2, 6-dimethylpyridine with various *N*-unprotected isatins bearing electron-withdrawing or electron-donating groups. In general, all the reactions proceeded smoothly to give the corresponding desired products in moderate-to-excellent yields. There was an apparent correlation between the efficiency of the reaction and the electronic property of the substituent. Isatins

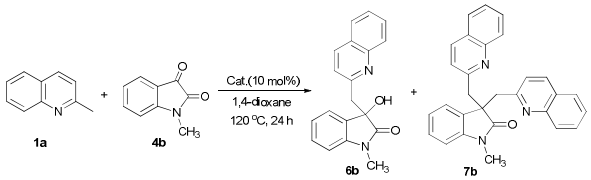


Scheme 3. *Reaction conditions*: 2, 6-dimethylpyridine **1i** (1.0 mmol), isatin **4** (0.4 mmol), $Fe(OAc)_2$ (10 mol%), 1,4-dioxane (1 mL), 120 °C, 24 h, isolated yield. [a] reaction time: 48 h.

bearing electron-withdrawing groups exhibited relatively higher productivity than did those with electron-donating substituents. For example, 7-trifluoromethyl derivative **4i** gave the product **5i** in 90% yield, whereas the electron-rich 5-methoxy derivative **4d** and 5-methyl derivative **4e** gave the corresponding products **5d** and **5e** in 59% and 64% yields, respectively, even if doubling the reaction time. This phenomenon might be ascribe to the enhancement of the electrophilicity of the carbonyl group of the isatin by electron-withdrawing groups. When the *N*-protected isatins **4b** and **4c** were subjected to this transformation, the protecting groups were found have no significant effect on the productivity of the reactions.

In the previous work about the synthesis of 3-azaarenylmethyl-3-hydroxy-2-oxindoles, the azaarenes were limited to pyridines. As shown in Table 2, Li et al. tried the reaction of 2-methylquinoline **1a** and *N*-methyl isatin **4b** catalyzed by TfOH, but the desired product 3-hydroxy-3-(quinolin-2-ylmethyl)indolin-2-one **6b** was not observed. Instead, the double addition product **7b** was isolated in 34% yield.[11a] Xiao et al. also tried the same reaction catalyzed by $Yb(OTf)_3$ and got the same result, only double addition product **6b** was isolated in 21% yield.[3j] Thus in situ generated product **6b** is proposed to undergo a subsequent dehydrative coupling reaction to furnish product **7b**. Encouraged by the success of iron-catalyzed addition reaction of methyl pyridines to isatins, we extended the scope of azaarenes to quinolines, and attempted the reaction of 2-methylquinoline **1a** with *N*-methyl isatin **4b** using iron (II) acetate as catalyst in 1,4-dioxane at 120 °C for 24 h. To our delight, the desired product **6b** was isolated in 49% yield, and the double addition product **7b** was not observed (entry 1), to the best of our knowledge, this is the first example to prepare 3-azaarenylmethyl-3-hydroxy-2-oxindoles from isatins and methyl quinolines. To improve the productivity, other iron salts of $FeCl_3$, $FeBr_3$, $Fe(OTf)_2$ and $Fe(acac)_3$ were screened. The results indicated that only $Fe(acac)_3$ was effective and gave the desired product **6b** in 44% yield (entries 2-5). Other metal salts, such as $Cu(OTf)_2$, $Sc(OTf)_3$,

Table 2 Catalyst screening for the reaction of 2-methylquinoline and *N*-methyl isatin [a]



Entry	Catalyst	**6b** (%)
1	$Fe(OAc)_2$	49
2	$FeBr_3$	0
3	$Fe(OTf)_2$	0
4	$Fe(acac)_3$	44
5	$FeCl_3$	0
6	$Cu(OTf)_2$	0
7	$Sc(OTf)_3$	0
8	$In(OTf)_3$	0
9[b]	$Fe(OAc)_2$	40
10[c]	$Fe(OAc)_2$	38

[a] *Reaction conditions*: 2-methylquinoline **1a** (1.0 mmol), *N*-methyl isatin **4b** (0.40 mmol), catalyst (10 mol%), 1,4-dioxane (1.0 mL), 120 °C, 24 h, N_2, isolated yield of **6b**, the product **7b** was not detected. [b]100 °C, 24 h; [c] 5 mol% $Fe(OAc)_2$, 120 °C, 24 h.

$In(OTf)_3$ were also subjected to this reaction, but no reaction occurred (entries 6-8). Lowering the reaction temperature and reducing the catalyst loading resulted in decreased yield (entries 9-10).

Under the optimized reaction conditions, the scope of the substrates were investigated. As shown in Scheme 4, the reaction of 2-methylquinoline **1a** with simple *NH* protic isatins gave the product **6a** in 60% yield. In contrast, when the *N*-substituted isatins were used as reaction partners, the corresponding products **6b** and **6c** were obtained in relatively lower yields. Next, we focused on the generality of the methyl quinolines, it was found that both electron-donating and electron-withdrawing groups (including halogen groups) at the phenyl ring of quinolines were well-

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tolerated in this reaction, and the desired products were isolated in moderate yields (**6d–6f**). 1-methylisoquinoline was also applicable to this transformation and provided the product **6g** in 60% yield. When 4-methylquinoline was subjected to the reaction with isatin, it proceeded successfully and furnished the product **6h** in 24% yield. The electron effect of isatins was also investigated, the results showed that electron-rich 5-methoxyisatin and electron-deficient 5-nitroisatin were tolerated in this transformation to give the desired products **6i** and **6j** in 37% and 35% yields, respectively.

6f: 57% **6g**: 60% **6h**: 24% **6i**: 37% **6j**: 35%

Scheme 4. *Reaction conditions*: methyl quinoline **1** (1.0 mmol), isatin **4** (0.40 mmol), $Fe(OAc)_2$ (10 mol%), 1,4-dioxane (1.0 mL), 120 °C, 24 h, N_2, isolated yield.

C(sp^3)–H Functionalization of Methyl Azaarenes with Aldehydes

Encouraged by the successful C(sp^3)–H functionalization of methyl azaarenes with glyoxylate, α- or β-ketoesters, isatins, and 1,2-dicarbonyls, the simple aldehydes were also subjected to this transformation. The reaction of 2-methylquinoline **1a** with benzaldehyde **8a** in the presence of various iron salts were investigated. As shown in Table 3, our preliminary experimental results indicated that iron(II) acetate was the best catalyst, and it gave the desired product 2-[(*E*)-2-phenylvinyl]quinoline **9aa** in 66% isolated yield when the reaction was performed at 120 °C for 24 hours (entries 1–6). ^{1}H NMR and GC/MS analyses of the product showed that the (*E*)-isomer was formed exclusively. These promising results encouraged us to optimize the reaction conditions with $Fe(OAc)_2$ as the catalyst. To our delight, the yields were markedly enhanced by the addition of a catalytic amount of a Brønsted acid such as methanesulfonic acid, triflic acid, 4-toluenesulfonic acid, acetic acid, or trifluoroacetic acid (TFA) as a co-catalyst (entries 7–11), and 98% yield of **9aa** was obtained in the presence of 10 mol% TFA. Next, we examined the effect of catalyst loading, **9aa** was isolated in 97% and 82% yields in the presence of 5% and 1 mol% of $Fe(OAc)_2$, respectively (entries 12 and 13). To confirm the role of the iron catalyst in this transformation, control experiments showed that **9aa** was obtained in 29% yield in the absence of $Fe(OAc)_2$ under otherwise identical conditions to entry 12, and only 18% yield of **9aa** was obtained in the absence of $Fe(OAc)_2$ and TFA. The results proved that iron(II) acetate was essential for high reactivity. Solvent screening showed that, of the solvents tested, toluene gave the best results (entries 12 and 16–18). Comparable yields were obtained at 120 °C and 100 °C (entries 12 and 19), but slightly lower yield was available at 80°C (entry 20). No effect was observed when the amount of benzaldehyde (**8a**) was reduced (entry 21).

Under the optimized reaction conditions, we examined the scope of the reaction of various aldehydes with 2-methylquinoline **1a**. Generally, as shown in Scheme 5, aldehydes bearing electron-donating or electron-withdrawing group at various positions on the aromatic ring were transformed into the desired (*E*)-2-alkenylazaarenes smoothly in good-to-excellent yields. The electron-deficient aldehydes **8j**–**8n** gave the desired products **9aj**–**9an** in high yields of 90–99%. In contrast, the electron-rich aldehydes **8p** and **8q** gave the corresponding products **9ap** and **9aq** in slightly lower yields of 89% and 85%, respectively. Interestingly, the reaction of **1a** with 4-acetylbenzaldehyde **8o** proceeded selectively to give 76% yield of product **9ao** with an intact acetyl group. Note that sterically hindered 2,6-dichlorobenzaldehyde **8f** also gave the desired product **9af** in 91% yield. 1-, and 2-naphthaldehydes (**8r** and **8s**, respectively) and the aromatic hetero aldehydes 2-furaldehyde **8t**, thiophene-2-carbaldehyde **8u**, pyridine-2-carbaldehyde **8v**, and nicotinaldehyde **8w** were also suitable for this transformation and gave the corresponding products **9ar**–**9aw** in 71–95% yields, which were superior to those previously reported.[10] To our delight, linear, secondary, and tertiary aliphatic aldehydes also underwent this transformation and gave the desired products **9ax**–**9az**, respectively, in moderate yields by increasing temperature and prolonging the reaction time.

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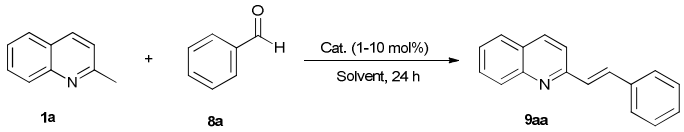
Table 3. Optimization of the reaction conditions[a]

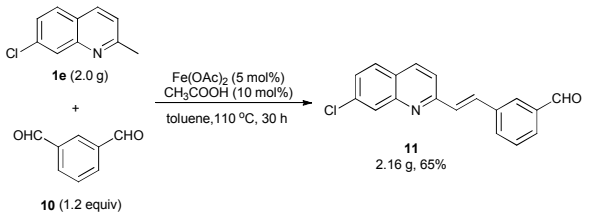


Entry	Catalyst (mol%)	Brønsted acid	Solvent	Temp. [°C]	Yield [%][b]
1	$FeCl_3$ (10)	–	toluene	120	40
2	$FeCl_2$ (10)	–	toluene	120	49
3	$Fe(ClO_4)_3.6H_2O$ (10)	–	toluene	120	42
4	$Fe(BF_4)_2.6H_2O$ (10)	–	toluene	120	55
5	$Fe(acac)_3$ (10)	–	toluene	120	37
6	$Fe(OAc)_2$ (10)	–	toluene	120	66
7	$Fe(OAc)_2$ (10)	$MeSO_3H$	toluene	120	70
8	$Fe(OAc)_2$ (10)	TfOH	toluene	120	82
9	$Fe(OAc)_2$ (10)	TsOH	toluene	120	80
10	$Fe(OAc)_2$ (10)	AcOH	toluene	120	84
11	$Fe(OAc)_2$ (10)	TFA	toluene	120	98
12	$Fe(OAc)_2$ (5)	TFA	toluene	120	97
13	$Fe(OAc)_2$ (1)	TFA	toluene	120	82
14	–	TFA	toluene	120	29
15	–	-	toluene	120	18
16	$Fe(OAc)_2$ (5)	TFA	1,4-dioxane	120	71
17	$Fe(OAc)_2$ (5)	TFA	$Cl(CH_2)_2Cl$	120	83
18	$Fe(OAc)_2$ (5)	TFA	MeCN	120	49
19	$Fe(OAc)_2$ (5)	TFA	toluene	100	97
20	$Fe(OAc)_2$ (5)	TFA	toluene	80	72
21[c]	$Fe(OAc)_2$ (5)	TFA	toluene	100	96

[a] *Reaction conditions*: 2-methylquinoline **1a** (0.4 mmol), benzaldehyde **8a** (0.6 mmol), Brønsted acid (0.04 mmol; entries 8–15, 17–22), solvent (1.0 mL), 24 h. [b] Isolated yield. [c] 0.48 mmol of benzaldehyde **2a** was used.

Next, we examined the scope of this transformation with regard to the 2-methylazaarene components. As shown in Scheme 5, the reactions of a series of 2-methylazaarenes **1b**–**1i** with benzaldehyde **8a** were examined under the optimized conditions. The reaction of benzaldehyde **8a** with quinolines **1b**–**1f** bearing election-deficient or electron-rich substituents on the benzene ring proceeded smoothly, to give the corresponding 2-alkenylquinolines **9ba**–**9fa** in 82–99% yield. 1-methylisoquinoline **1h** similarly gave the alkenyl derivative **9ha** in 85% yield, and 2-methylquinoxaline **1g**, gave 2-[(*E*)-2-phenylvinyl]quinoxaline **9ga**, albeit in slightly lower yield. In addition, 2,6-dimethylpyridine **1i** gave the desired product **9ia** in 35% yield at a higher temperature and with a longer reaction time, whereas 2-methylpyridine did not give any product, possibly as a result of the electronic effect of the methyl group on the pyridyl ring.

Finally, we applied this attractive protocol to the synthesis of 3-[(*E*)-2-(7-chloroquinolin-2-yl)vinyl]benzaldehyde **11**, a key intermediate in the synthesis of leukotriene receptor antagonist Montelukast (Singulair). Compound **11** is usually prepared in 45–65% yield by the reaction of 7-chloro-2-methylquinoline **1e** and isophthalaldehyde **10** promoted by a stoichiometric amount of acetic acid or acetic anhydride.[17] The use of large amounts of acetic acid or acetic anhydride in manufacture is very inconvenient, making the process uneconomical. In addition, acetic anhydride is a regulated commercial item, as it is widely used in the production of illicit narcotics. As shown in Scheme 6, when the gram-scale reaction of chloro compound **1e** with isophthalaldehyde **10** catalyzed by 5 mol% $Fe(OAc)_2$ was performed in the presence of a catalytic amount of acetic acid in toluene at 110 °C for 30 h, the desired compound **11** was obtained in 65% yield, which is comparable to the best result yet reported.



Scheme 6. Gram-scale synthesis of the intermediate of Montelukast

The proposed reaction pathway for the addition of 2-methyl azaarenes to carbonyl compounds was described in Scheme 7. The acidity of $C(sp^3)$–H bond of 2-methyl quinoline **1a** should be significantly enhanced upon ligation to iron to form complex **A**. Driven by the endogenous basic OAc^- anion abstraction, C–H cleavage is known to occur to give iron-enamide species **B**. On the one hand, the active iron-enamide species **B** undergo nucleophilic attack to the proton activated aldehyde **8** to form intermediate **D**, in which the endogenous basic anion OAc^- abstract the proton, giving compound **9** via an *E2*-elimination process in high stereoselectivity with regenerated iron catalyst. On the other hand, when the active iron-enamide species **B** undergo nucleophilic attack to 1,2-dicarbonyl compound **2**, the electrophilicity of the carbonyl group is dramatically enhanced by

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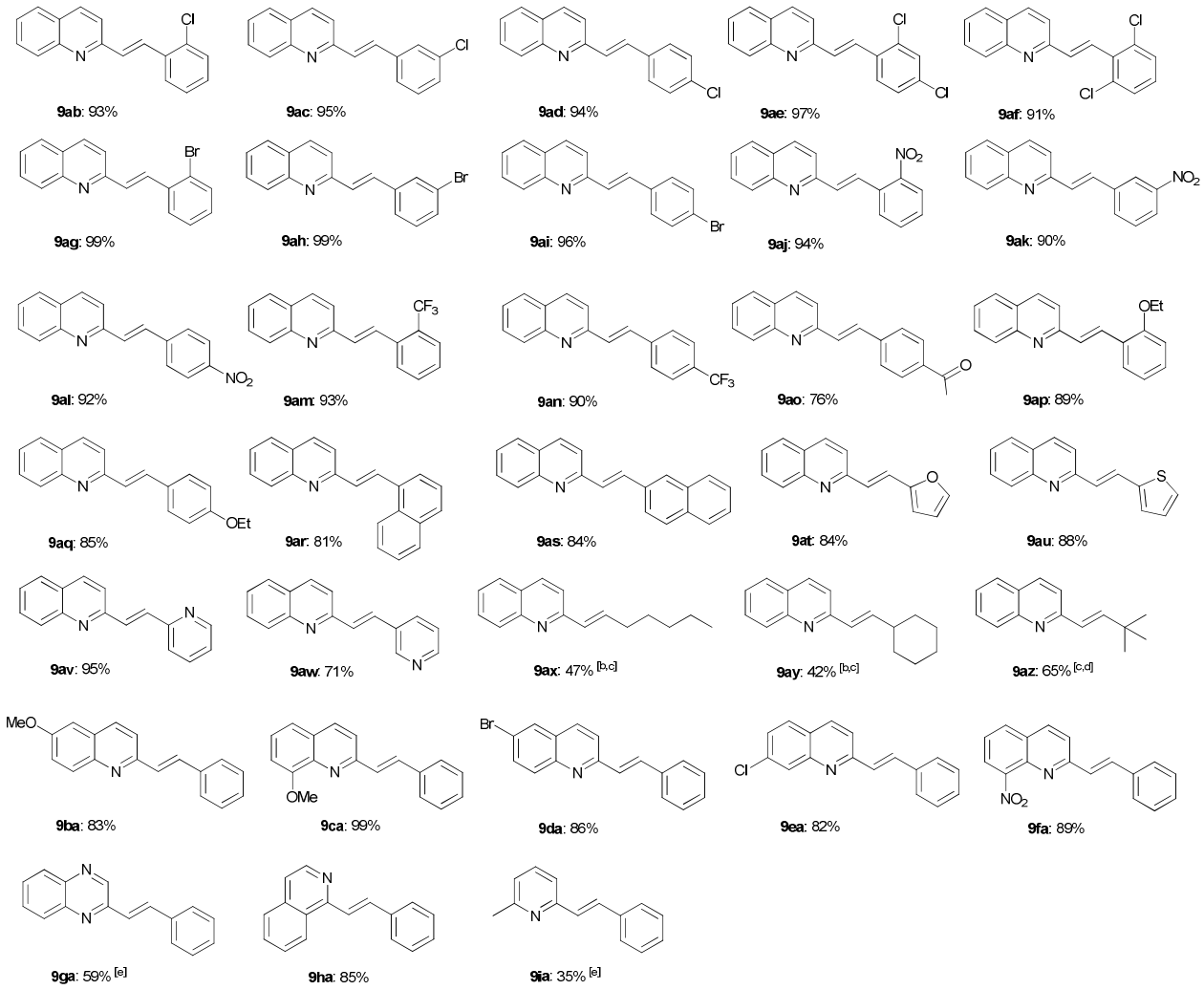
the complexation of carbonyl groups with iron, to give intermediate **F** via a transition state **E**. The compound **3** is formed with regenerated iron catalyst after hydrolysis of intermediate **F**.



Scheme 5. Substrate scope of aldehydes and methyl azaarenes. *Reaction conditions*: methyl azaarene **1** (0.4 mmol), aldehyde **8** (0.48 mmol), $Fe(OAc)_2$ (5 mol%), TFA (10 mol%), toluene (1.0 mL), 100 °C, 24 h, isolated yield. The *E*-isomer was obtained exclusively in all cases. [a] Reaction temperature: 120 °C; [b] Reaction time: 36 h; [c] 1.0 mmol pivaldehyde **2z** was used; [d] 140 °C for 48 h.

Conclusions

In summary, we have developed an iron-catalyzed atom-, step-economic green synthesis of azaarene-substituted *α*- or *β*-hydroxy carboxylic esters, 3-azarenylmethyl-3-hydroxy-2-oxindoles, and *trans*-2-alkenylazaarenes via $C(sp^3)$–H bond functionalization of methyl azaarenes with carbonyl compounds. The investigation of detailed reaction mechanism of iron-catalyzed $C(sp^3)$–H bond functionalization and their asymmetric variants are currently underway.

Experimental Section

General Remarks: All the experiments were performed under nitrogen in standard Schlenk tubes. All chemicals and solvents were purchased from commercial suppliers and were used without further purification. 1-Methyl- and 1-Benzyl-1*H*-indole-2,3-diones were prepared according to the literature method. NMR spectra were recorded at 25 °C by using a JEOL JNM-A500 spectrometer (500 MHz for ^1H, 125 MHz for ^{13}C). Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard. Chemical shifts of ^{13}C NMR are reported relative to the solvent peak as an internal standard. Mass spectra were recorded with a JEOL AccuTOF GC JMS-T100GC equipped with Agilent 6890N GC or a JEOL AccuTOF JMS-T100LC. Melting points were determined by using a Yanaco MP-J3 micro melting-point apparatus and are uncorrected.

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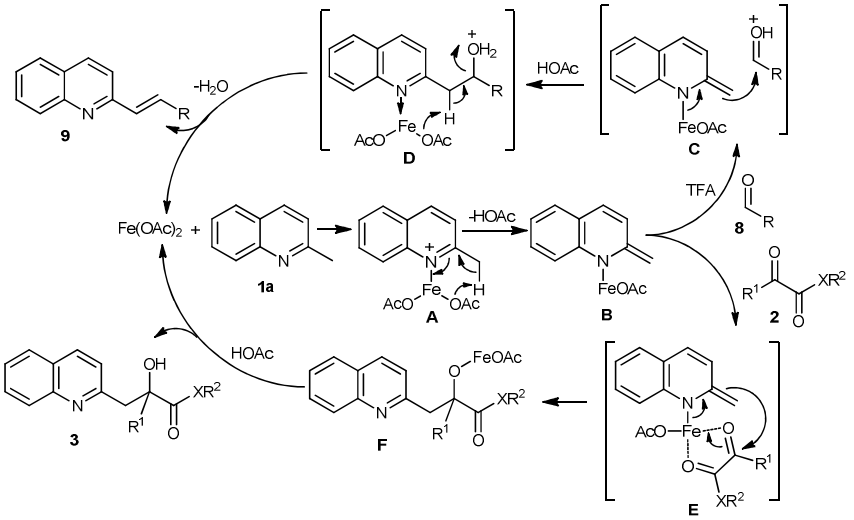

Scheme 7. Proposed reaction pathway for the addition of 2-methyl azaarenes and carbonyl compounds

Typical Procedure for the Synthesis of Azaarene-Substituted Lactate Derivatives, Exemplified by the Synthesis of Ethyl 2-Hydroxy-3-quinolin-2-ylpropanoate (3aa): $Fe(OAc)_2$ (3.5 mg, 0.02 mmol), 2-methylquinoline **1a** (1.0 mmol), and ethyl glyoxylate **2a** (0.4 mmol) were dissolved in 1,4-dioxane (1.0 mL) under N_2, and the mixture was stirred at 120 °C for 24 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel) to give a **3aa** as a white solid: yield: 97 mg (90%); mp: 112-115 °C; IR (ATR, neat) ν = 626, 763, 831, 1040, 1161, 1287, 1508, 1599, 1732, 2979, 3065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.5 Hz, 3H, CH_3), 3.39-3.52 (m, 2H, CH_2), 4.22 (q, J = 7.5 Hz, 2H, CH_2), 4.77 (dd, J_1 = 7.5 Hz, J_2 = 3.5 Hz, 1H, CH), 7.31 (d, J = 8.5 Hz, 1H, ArH), 7.51-7.53 (m, 1H, ArH), 7.68-7.72 (m, 1H, ArH), 7.79 (d, J = 8.0 Hz, 1H, ArH), 8.00 (d, J = 8.0 Hz, 1H, ArH), 8.11 (d, J = 9.0 Hz, 1H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 40.9, 61.3, 70.4, 122.0, 126.2, 126.9, 127.5, 128.7, 129.7, 136.7, 147.1, 158.8, 173.6 ppm; EI-HR-MS: m/z = 268.0952, calcd. for $C_{14}H_{15}NNaO_3$ $[M+Na]^+$: 268.0950.

Typical Procedure for the Synthesis of 3-Azaarene-Substituted-3-Hydroxy-2*H*-indol-2-ones, Exemplified by the Synthesis of 3-Hydroxy-3-[(6-methyl pyridin-2-yl)methyl]-7-(trifluoromethyl)-1,3-dihydro-2*H*-indol-2-one 5i: $Fe(OAc)_2$ (7.0 mg, 0.04 mmol), 7-(trifluoromethyl)-1*H*-indole-2,3-dione **4i** (0.4 mmol), and 2,6-dimethylpyridine **1i** (1.0 mmol) were dissolved in 1,4-dioxane (1.0 mL) under N_2, and the mixture was stirred at 120 °C for 24 h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was then purified by flash column chromatography (silica gel) to give **5i** as a light-yellow solid; yield: 124 mg (90%). mp: 166-168 °C; IR (ATR, neat) ν = 711, 814, 1110, 1342, 1458, 1623, 1735, 3125, 3238 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.61 (s, 3H, CH_3), 3.07 (d, J = 15.0 Hz, 1H, CH_2), 3.28 (d, J = 15.5 Hz, 1H, CH_2), 6.88 (d, J = 7.0 Hz, 1H, ArH), 6.97-7.03 (m, 2H, ArH), 7.16 (d, J = 8.0 Hz, 1H, ArH), 7.42 (d, J = 7.0 Hz, 1 H, ArH), 7.57 (t, J = 7.5 Hz, 1H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 42.1, 75.4, 111.9, 112.1, 112.4, 121.5, 122.1, 122.4, 122.6, 124.8, 125.8, 125.9, 126.0, 127.6, 133.2, 137.5, 137.6, 156.2, 157.3, 178.2 ppm; ESI-HR-MS: m/z =345.0816, calcd. for $C_{16}H_{13}F_3N_2NaO_2$ $[M+Na]^+$:345.0826.

Typical Procedure for the Synthesis of (*E*)-2-Alkenylazaarenes, Exemplified by the Synthesis of 2-[(*E*)-2-Phenylvinyl]quinoline (9aa): $Fe(OAc)_2$ (3.5 mg, 0.02 mmol), 2-methylquinoline **1a** (58 mg, 0.4 mmol), PhCHO **8a** (51 mg, 0.48 mmol), and TFA (3 μL, 0.04 mmol) were dissolved in dry toluene (1.0 mL) under N_2 and the mixture was stirred at 100 °C for 24 h. The mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel) to give **9aa** as a white solid; yield: 89 mg (96%). mp: 99-101°C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32-7.52 (m, 5H, ArH), 7.64-7.73 (m, 5H, ArH), 7.79 (d, J = 8.0 Hz, 1H, CH), 8.08 (d, J = 8.0 Hz, 1H, CH), 8.14 (d, J = 8.5 Hz, 1H, ArH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 119.2, 126.1, 127.2, 127.3, 127.5, 128.6, 128.8, 129.0, 129.2, 129.7, 134.4, 136.3, 136.5, 148.3, 156.0 ppm; EI-HR-MS: m/z = 231.1054, calcd. for $C_{17}H_{13}N$: 231.1048.

Gram-Scale Synthesis of 3-[(*E*)-2-(7-Chloroquinolin-2-yl)vinyl] benzaldehyde (11): A solution of 7-chloro-2-methylquinoline (**1e**; 2.0 g, 11.26 mmol), isophthalaldehyde **10** (1.80 g, 13.4 mmol), $Fe(OAc)_2$ (98 mg, 0.56 mmol), and AcOH (65 μL, 1.13 mmol) in toluene (12 mL) was stirred at 110 °C for 30 h while the reaction was monitored by TLC. The mixture was then allowed to cool to room temperature and the precipitated crude solid was recovered by filtration. The wet crude solid was added to EtOAc (60 mL) and the mixture was refluxed with stirring for 2 h. The mixture was then filtered and the filtrate was concentrated to 10 mL. The resultant slurry was cooled to 0 °C with stirring for 3 h. The solid that separated was collected by filtration, washed with chilled EtOAc, and dried under vacuum to give **11** a light-yellow solid; yield: 2.16 g (65%). mp: 150-152 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45-7.49 (m, 2H, ArH), 7.59 (t, J = 8.0 Hz, 1H, ArH), 7.64 (d, J = 9.0 Hz, 1H, CH), 7.74 (d, J = 8.5 Hz, 1H, ArH), 7.81 (d, J = 16.5 Hz, 1H, CH), 7.85 (d, J = 7.5 Hz, 1H, ArH), 7.90 (d, J = 7.5 Hz, 1H, ArH), 8.10-8.15 (m, 3H, ArH), 10.08 (s, 1H, CHO) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 119.9, 125.8, 127.3, 128.1, 128.2, 128.7, 129.5, 129.7, 130.1, 132.9, 133.4, 135.7, 136.3, 136.9, 137.3, 148.6, 156.1,192.0 ppm; EI-HR-MS: m/z = 293.0615, calcd. for $C_{18}H_{12}ClNO$: 293.0607.

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Entry for the Table of Contents

Iron-Catalyzed C(sp^3)–H Functionalization of Methyl Azaarenes: A Green Approach to Azaarene-substituted α- or β-Hydroxy Carboxylic Derivatives and 2-Alkenylazaarenes

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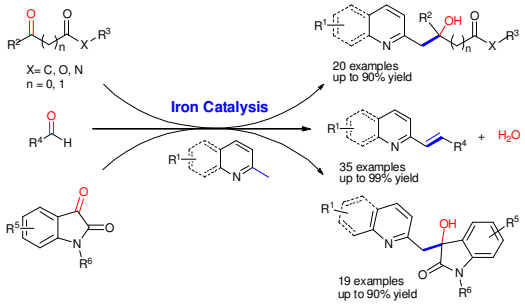

An iron-catalyzed C(sp3)–H functionalization of methyl azaarenes with carbonyls to access the title compounds have been described.

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