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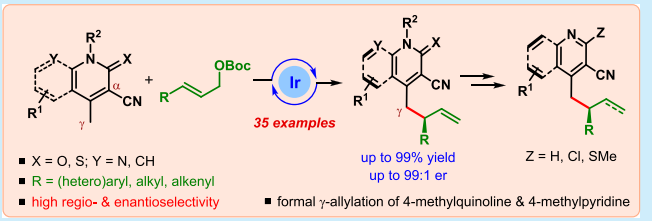
Enantioselective Direct Vinylogous Allylic Alkylation of 4-Methylquinolones under Iridium Catalysis

Rahul Sarkar and Santanu Mukherjee*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

Supporting Information

ABSTRACT: The first enantioselective vinylogous allylic alkylation of 4-methylquinolones has been developed. This iridium-catalyzed reaction introduces an allyl group at the γ-position of 4-methyl-2-quinolones with exclusive branched selectivity and an excellent level of enantioselectivity. This in turn allows for the enantioselective synthesis of γ-allylquinolines and related nitrogenous heterocycles. This is the first application of 4-methylquinolones in an enantioselective transformation.



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Ever since the first reports by Takeuchi[1] and Helmchen[2] in 1997, iridium-catalyzed allylic substitution reactions have been identified among the most versatile and reliable methods for the enantioselective construction of carbon−carbon and carbon−heteroatom bonds.[3] Tremendous developments, especially in the realm of catalyst design, took place during the past two decades, primarily due to the works of Hartwig,[4] Carreira,[5] and You,[6] and led to the invention of a plethora of enantioselective transformations involving direct carbon- and heteroatom-centered nucleophiles.[3] In contrast, the application of vinylogous nucleophiles in Ir-catalyzed allylic alkylation remain rather subdued.

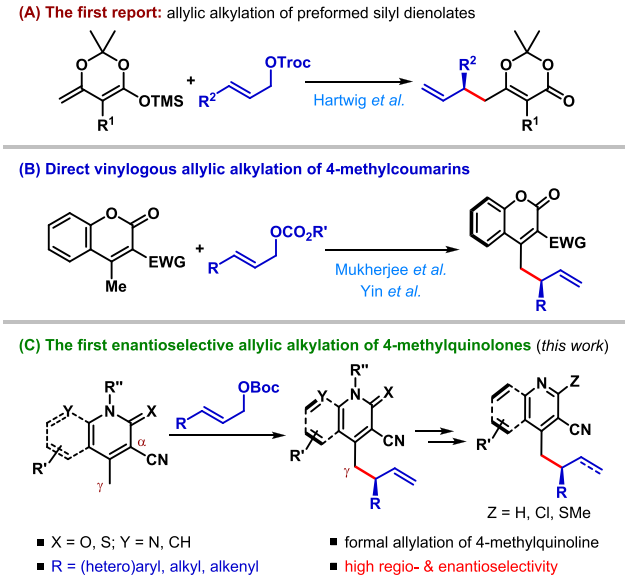
It was only in 2014 that Hartwig et al. developed the first Ir-catalyzed vinylogous allylic alkylation using preformed silyl dienolates as the nucleophile (Scheme 1A).[7] Subsequent to this report, Ir-catalyzed direct vinylogous allylic alkylation of α,β-unsaturated carbonyl compounds was developed by the Jørgensen[8] and Stoltz groups.[9] Very recently, our laboratory[10] and subsequently Yin et al.[11] developed the first Ir-catalyzed enantioselective vinylogous allylic alkylation of 4-methylcoumarins (Scheme 1B).

While contemplating the idea of exploring the aza-analogue of 4-methylcoumarins as potential vinylogous nucleophiles, we realized that 4-methylquinolones have never been used as vinylogous nucleophiles in any enantioselective transformations. In fact, application of either 2-quinolones themselves or their derivatives in enantioselective transformations remains extremely rare. The only known catalytic enantioselective transformations of 2-quinolone consist of [2 + 2]-photocycloadditions with olefins, catalyzed by thioxanthone as chiral sensitizer, pioneered by Bach et al.[12,13] Apart from [2 + 2]-photocycloadditions, no other enantioselective transformation of 2-quinolones is reported to date.[14]

Considering the rich biomedical and pharmaceutical importance of 2-quinolones,[15] we envisioned that the introduction of a chiral center around the 2-quinolone framework would create an additional chemical space for its structural modification. In addition, the lack of literature reports on the vinylogous reactivity of 4-methylquinolones made us wonder about their electronic properties, despite structural similarity with 4-methylcoumarins.

Following our recent works on the vinylogous allylic alkylation of 4-methylcoumarins,[10,16] we surmised that iridium-catalyzed asymmetric allylic alkylation would be a perfect platform to test the electronic properties of 4-methylquinolones and at the same time to install a stereocenter

Scheme 1. Ir-Catalyzed Enantioselective Vinylogous Allylic Alkylation



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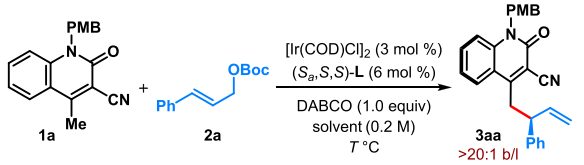
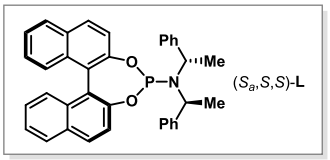
around 2-quinolone without disturbing its core structure (Scheme 1C).

Herein, we report the results of this investigation in the form of the first catalytic enantioselective vinylogous allylic alkylation of 4-methylquinolones.

Choice of a suitable *N*-protecting group which can be easily removed after the γ-allylation was a prime concern at the outset of our investigation. Following a few preliminary experiments,[17] *p*-Methoxybenzyl (PMB)-protected 3-cyano-4-methylquinolin-2(1*H*)-one **1a** was selected as the model substrate for reaction with *tert*-butyl cinnamyl carbonate **2a** (Table 1). In the presence of DABCO as an external base to

Table 1. Optimization of Reaction Parameters[a]





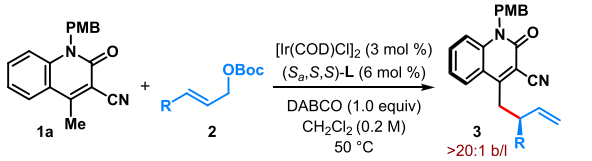
	1a/2a	solvent	*T* (°C)	*t* (h)	yield[b] (%)	er[c]
1	1:1.2	$(CH_2Cl)_2$	50	72	35	98:2
2	1:1.2	CH_2Cl_2	50	21	90 (90)	98:2
3	1:1.2	CH_2Cl_2	25	72	15	97:3
4	1.2:1	CH_2Cl_2	50	6	78	98:2
5[d]	1:1.2	CH_2Cl_2	50	24	94 (94)	98:2

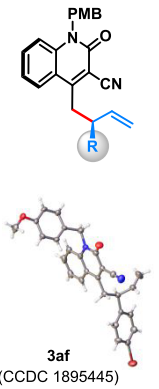
[a]Reaction conditions: 3 mol % of $[Ir(COD)Cl]_2$, 6 mol % of **L**, 0.10 mmol of **1a**, 0.12 mmol of **2a**, and 0.10 mmol of DABCO in 0.5 mL of solvent. The catalyst was prepared via *n*-$PrNH_2$ activation. [b]Yields were determined by ^1H NMR spectroscopy with mesitylene as internal standard. Isolated yields are given in the parentheses. [c]Enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase. [d]1.5 mol % of $[Ir(COD)Cl]_2$, 3 mol % of ligand, 0.20 mmol of **1a**, 0.24 mmol of **2a**, and 0.20 mmol of DABCO in 1.0 mL of solvent.

enolize **1a**, a combination of 3 mol % of $[Ir(COD)Cl]_2$ and 6 mol % of Feringa's phosphoramidite ligand[18] (S_a,*S*,*S*)-**L** was first tested as precatalyst for the reaction in 1,2-dichloroethane at 50 °C. To our delight, the reaction was found to proceed in the expected fashion to generate the desired γ-allylated 2-quinolone **3aa** exclusively as a single regioisomer (>20:1 b/l) with high enantioselectivity, albeit in only 35% yield (entry 1). Changing the reaction medium from 1,2-dichloroethane to dichloromethane significantly improved the yield as well as the rate of the reaction (entry 2). Performing the reaction at 25 °C (entry 3) or increasing the amount of **1a** (entry 4) adversely affected the reaction efficacy. The loading of $[Ir(COD)Cl]_2$ and ligand **L** could be reduced to 1.5 and 3 mol %, respectively, without any negative influence on either yield or er (entry 5).

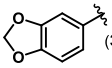
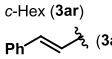
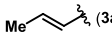
Having optimized the reaction conditions (Table 1, entry 2),[19] we sought to test the scope and limitations of this enantioselective γ-allylation reaction. As depicted in Table 2, our protocol is quite general and can be applied to a wide variety of allylic carbonates. 4-Methylquinolone **1a** underwent facile γ-allylic alkylation with cinnamyl carbonates (**2a**–**k**)

Table 2. Scope of the Enantioselective Allylic Alkylation with Regard to Allylic Carbonates[a]





3af
(CCDC 1895445)

entry	R (3)	*t* (h)	yield (%)	er
1	Ph (**3aa**)	21	90	98:2
2	4-MeC_6H_4 (**3ab**)	24	82	98:2
3	4-(*i*-Pr)C_6H_4 (**3ac**)	42	91	98:2
4	4-$OMeC_6H_4$ (**3ad**)	20	98	98:2
5	4-$CF_3C_6H_4$ (**3ae**)	45	56	98:2
6	4-BrC_6H_4 (**3af**)	48	98	98:2[b]
7	4-ClC_6H_4 (**3ag**)	12	88	98:2
8	3-BrC_6H_4 (**3ah**)	42	70	98:2
9	3-FC_6H_4 (**3ai**)	48	48	98:2
10	2-Naphth (**3aj**)	42	98	98:2
11	3,4-$Cl_2C_6H_3$ (**3ak**)	66	79	98:2
12	 (**3al**)	45	98	98:2
13	3-Pyr (**3am**)	67	69	n.d.
14	2-Furyl (**3an**)	64	90	98.5:1.5
15	2-Thienyl (**3ao**)	48	79	99:1
16	Et (**3ap**)	72	83	97:3
17	Bn (**3aq**)	72	50	n.d.
18	*c*-Hex (**3ar**)	72	49	92.5:7.5
19	 (**3as**)	64	98	98:2
20	 (**3at**)	67	91	96:4

[a]Reaction conditions: 3 mol % of $[Ir(COD)Cl]_2$, 6 mol % of **L**, 0.20 mmol of **1a**, 0.24 mmol of **2**, and 0.20 mmol of DABCO in 1.0 mL of CH_2Cl_2. The catalyst was prepared via *n*-$PrNH_2$ activation. Yields correspond to the isolated product after chromatographic purification. The er was determined by HPLC analysis on a chiral stationary phase. [b]The product **3af** was obtained with 99.5:0.5 er after a single recrystallization. n.d. = not determined.

having either electron-withdrawing or electron-donating substituents at various positions of the aryl ring to generate the products with good to high yield and uniformly high enantioselectivity (entries 1–11). In the case of *p*-bromophenyl-substituted allylic carbonate **2f**, nearly enantiopure product **3af** could be obtained after a single recrystallization. Single-crystal X-ray diffraction analysis of **3af** revealed its absolute configuration to be (*S*) (CCDC 1895445; Table 2). The configurations of the other products were assigned by analogy as the same. Pharmaceutically relevant heterocycles were successfully incorporated into the products. Such examples include dioxolane (**3al**), pyridine (**3am**), furan (**3an**), and thiophene (**3ao**), which were formed with high er (entries 12–15).

The efficacy of our protocol is not restricted to aryl- or heteroaryl-substituted allylic carbonates. Alkyl- and alkenyl-substituted allylic carbonates also effectively participated in the reaction. Allylic carbonates bearing a linear alkyl group (**2p**) and benzyl group (**2q**) provided the products with moderate to good yield and high enantioselectivity (entries 16 and 17). Product containing a branched alkyl group (**3ar**) was formed in moderate yield and with good er (entry 18). Alkenyl-substituted allylic carbonates (**2s** and **2t**) resulted in γ-allylated 2-quinolones (**3as** and **3at**) as a single regioisomer with high yield and er (entries 19–20).

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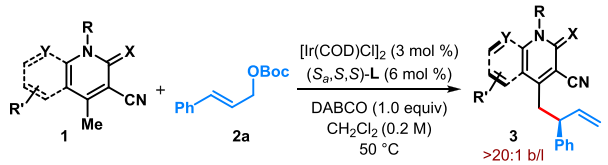
After successfully showcasing the scope with respect to allylic carbonates, we turned our attention to 2-quinolones bearing substituents on the aryl ring for reaction with cinnamyl carbonate **2a** (Table 3A). *N*-Protected 3-cyano-4-methyl-2-quinolones bearing substituents of diverse electronic demand on the aromatic ring (**1b**–**i**) were well tolerated, furnishing the products generally in high yield and with good to high enantioselectivity (entries 1–8). Irrespective of the electronic nature of the substituent on the 7-position of the quinolone moiety, products (**3ca** and **3ha**) were obtained only with moderate enantioselectivity (entries 2 and 7).

The effect of the *N*-substituent on 2-quinolone was also investigated (Table 3A). The *p*-methoxybenzyl group can be replaced with simple alkyl (**1j**–**1k**), benzyl (**1l**), and even with allyl (**1m**) groups without compromising either yield or enantioselectivity (entries 9–12). However, the vinylogous reactivity of quinolone was completely switched off when unprotected 2-quinolone (**1n**) was employed (entry 13). Instead of the desired γ-allylated product, this reaction resulted in exclusive *N*-allylation.[17] The above observations clearly imply that the presence of a suitable *N*-protecting group is necessary for 2-quinolones to exert its vinylogous reactivity. *N*-Protected 4-methyl-2-quinolones with other electron-withdrawing substituents such as ester, amide, or ketone at the 3-position turned out to be completely unreactive under our optimized reaction conditions.[17]

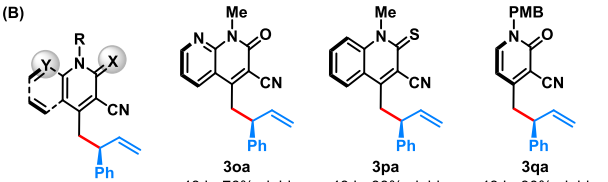
Table 3. Scope of the Enantioselective Allylic Alkylation with Respect to 2-Quinolones[a]



(A)

entry	R	R' (3)	t (h)	yield (%)	er
1	PMB	6-Me (**3ba**)	72	79	97.5:2.5
2[b]	PMB	7-Me (**3ca**)	60	81	89.5:10.5
3	PMB	6-OMe (**3da**)	72	84	97:3
4	PMB	6-F (**3ea**)	48	98	96.5:3.5
5	PMB	6-Cl (**3fa**)	46	99	98:2
6	PMB	6-Br (**3ga**)	46	96	98:2
7	PMB	7-CF_3 (**3ha**)	55	91	88:12
8	Me	6-NO_2 (**3ia**)	48	86	98:2
9	Me	H (**3ja**)	24	92	98:2
10	Et	H (**3ka**)	48	99	98:2
11	Bn	H (**3la**)	48	92	98:2
12	Allyl	H (**3ma**)	48	98	98:2
13	H	H (**3na**)	48	<5	–

(B)



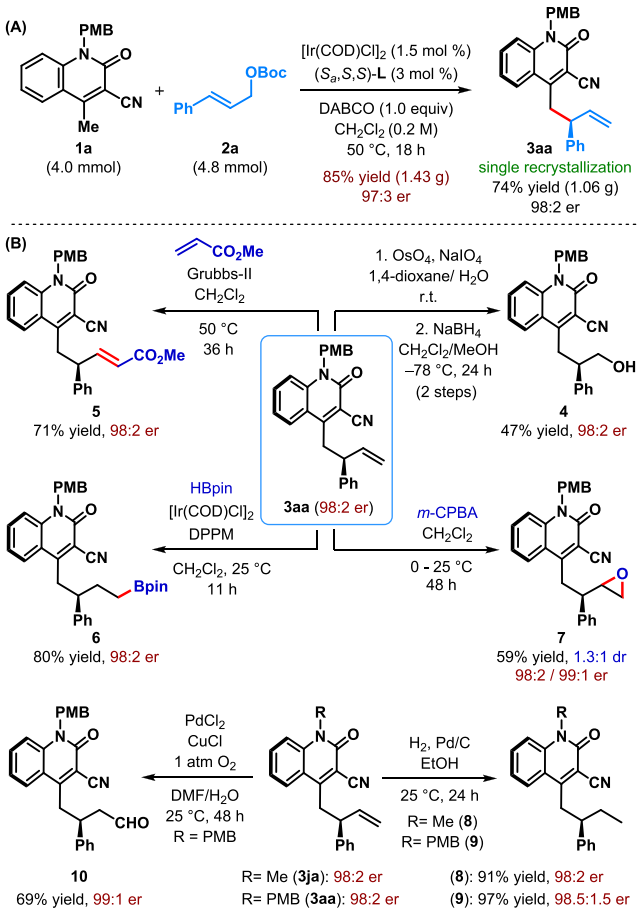
[a]Reaction conditions: 3 mol % of $[Ir(COD)Cl]_2$, 6 mol % of **L**, 0.20 mmol of **1a**, 0.24 mmol of **2a**, and 0.20 mmol of DABCO in 1.0 mL of CH_2Cl_2. The catalyst was prepared via *n*-$PrNH_2$ activation. Yields correspond to the isolated product after chromatographic purification. The er was determined by HPLC analysis on a chiral stationary phase. [b]Reaction performed on a 0.10 mmol scale of **1c**.

Attempted allylic alkylation of 3-cyano-4-ethyl-2-quinolone under our optimized reaction conditions resulted in the formation of a nearly equimolar mixture of branched/linear γ-allylated products, and the brached product was formed as 1.1:1 dr.[17]

The applicability of the present catalytic system was tested on other structurally related cyclic amides and even to thioamide (Table 3B). 1,8-Naphthyridin-2-one derivative **1o** reacted efficiently to give the product **3oa** with high yield and er. A similar level of enantioselectivity was observed in the case of cyclic thioamide **1p**. In addition, our protocol could be extended to 2-pyridone derivative **1q**. Although the product **3qa** was formed with only 30% yield, the reaction proceeded with very high enantioselectivity.

To demonstrate the practicality of our protocol, a gram-scale synthesis of **3aa** was carried out with 1.5 mol % of $[Ir(COD)Cl]_2$ to obtain the product in 85% yield and 97:3 er (Scheme 2A). The enantiopurity of the product could be improved to 98:2 er by a single recrystallization.

Scheme 2. (A) Gram-Scale Synthesis and (B) Synthetic Elaboration of γ-Allyl-2-quinolone 3aa



The synthetic utility of the γ-allylated 2-quinolones, obtained through direct vinylogous allylic alkylation, was displayed by converting the newly installed allylic unit into various synthetically important functionalities (Scheme 2B). Oxidative cleavage of olefin under OsO_4–$NaIO_4$ generated the corresponding aldehyde from **3aa**, which was isolated as the alcohol **4** in 47% yield over two steps. Olefin cross-metathesis of **3aa** with methyl acrylate in the presence of Grubbs' second-

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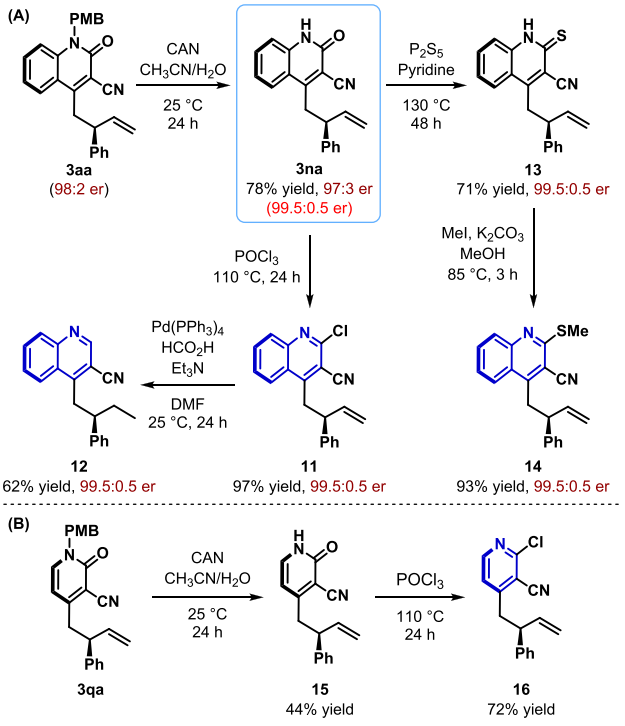
generation catalyst furnished the ester **5** in 71% yield. Ir-catalyzed hydroboration[20] of the terminal double bond in **3aa** provided the alkyl borate **6** in 80% yield. Epoxidation of **3aa** using *m*-CPBA afforded the epoxide **7** in 59% yield, albeit with poor diastereoselectivity (1.3:1 dr). Selective hydrogenation of the terminal double bond could be achieved efficiently using catalytic Pd/C as shown for **3ja** and **3aa**. Importantly, in the case of **3aa**, the PMB group survived under these conditions. When subjected under Wacker oxidation conditions,[21] **3aa** surprisingly resulted in the formation of aldehyde **10** in 69% yield. In all these cases, the products were isolated without any erosion in enantiopurity.

The quinoline ring tethered with a chiral center is a very important structural unit found in many chiral quinoline alkaloids (including *Cinchona* alkaloids) with interesting pharmacological as well as biological properties.[22] However, enantioselective synthesis of quinolines bearing a stereocenter outside the aromatic ring is a challenging task.[23] We realized that this vinylogous allylic alkylation reaction could be applied to address this issue.

Toward this goal, the PMB group in **3aa** was successfully removed using ceric ammonium nitrate (CAN) to give the unprotected lactam (**3na**) in 78% yield (Scheme 3A). A single

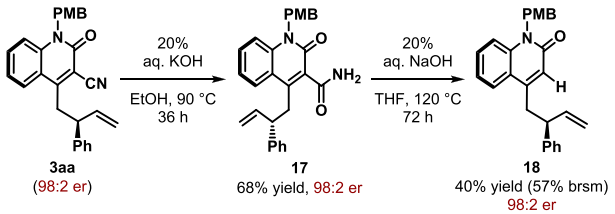
Scheme 3. (A) Removal of Protecting Group and Synthesis of Enantioenriched Quinolines. (B) Synthesis of γ-Allyl-2-chloropyridine 16



recrystallization led to enantiopure **3na**, which was used for the synthesis of quinoline derivatives. Treatment of **3na** with $POCl_3$ under reflux generated γ-allyl-2-chloroquinoline **11** in 97% yield. Dechlorination as well as hydrogenation of the terminal double bond took place when **11** was treated with triethylammonium formate in the presence of $Pd(PPh_3)_4$ to furnish γ-alkylquinoline **12** in 62% yield. Reaction of **3na** with P_2S_5 in basic medium furnished thiolactam **13** in 71% yield. Methylation of **13** afforded γ-allyl-2-thiomethylquinoline **14** in 93% yield. Compounds **11**, **12**, and **14** would be difficult to synthesize by other means, thereby highlighting the power of this protocol. As a proof of principle, formal γ-allylation of 4-methylpyridine could also be achieved via a two-step sequence starting from **3qa**. Deprotection of the PMB group in **3qa** resulted in the formation of γ-allyl-2-pyridone **15** in 44% yield, which was reacted with $POCl_3$ under reflux to produce γ-allyl-2-chloropyridine **16** in 72% yield (Scheme 3B). This reaction sequence compliments the enantioselective Ir-catalyzed allylic alkylation of 2-methylpyridines developed by You et al.[24]

The presence of the cyano group at the 3-position of quinolones appears to be a prerequisite for its vinylogous reactivity and at the same time marks a limitation of this protocol. However, the cyano group in the product (**3aa**) can be hydrolyzed to the corresponding amide (**17**) under aqueous KOH in EtOH at 90 °C (Scheme 4). Subjecting **17** to

Scheme 4. Synthesis of α-Unsubstituted γ-Allylquinolone 18



refluxing aqueous NaOH in THF led to the decarboxylation and furnished α-unsubstituted γ-allylquinolone **18**. Enantiopurity of **3aa** was maintained during this reaction sequence.

In conclusion, we have developed the first enantioselective vinylogous allylic alkylation of 4-methylquinolones. Using easily accessible linear allylic carbonates as the allylic electrophile, this Ir/phosphoramidite-catalyzed reaction delivers γ-allylated 2-quinolones generally in very high yield with exclusive regioselectivity (b vs l) and excellent level of enantioselectivity. This is the first time 4-methylquinolones have been used in an enantioselective transformation. Synthetic applicability of our protocol has been demonstrated by converting the products into a number of useful structural motifs containing diverse functional groups. Enantioselective synthesis of chiral quinoline and pyridine derivatives achieved through structural modification of the products also illustrates the potential of this γ-allylic alkylation reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01934.

Experimental details and characterization data (PDF)

NMR spectra and HPLC chromatograms (PDF)

Accession Codes

CCDC 1895445 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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AUTHOR INFORMATION

Corresponding Author

*E-mail: sm@iisc.ac.in.

ORCID

Rahul Sarkar: 0000-0003-3700-6580

Santanu Mukherjee: 0000-0001-9651-6228

Notes

The authors declare no competing financial interest.

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