Catalytic Enantioselective Friedel-Crafts Allenylic Alkylation

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Abstract: The first catalytic enantioselective Friedel-Crafts (FC) allenylic alkylation for the creation of central chirality has been developed under cooperative Ir(I)/(phosphoramidite,olefin) and Lewis acid catalysis. Using racemic allenylic alcohol as the electrophile, this enantioconvergent reaction proceeds through an Ir(I)-stabilized allenylic carbocation intermediate, which is intercepted with a variety of electron-rich arenes and heteroarenes. The resulting highly enantioenriched (up to >99.5:0.5 er) 1,1-disubstituted allenylic methanes, bearing a benzylic carbon stereocenter, are obtained with complete regiocontrol – both on (hetero)arenes as well as on the allenylic fragment. This protocol allows for the enantioselective formal introduction of 4-carbon alkane chains into (hetero)arenes with the creation of a benzylic stereocenter. An intramolecular version of this FC allenylic alkylation has also been shown to proceed with promising enantioselectivity under the same catalytic conditions.

Enantioselective introduction of an unfunctionalized alkyl group into (hetero)arenes is an important transformation, owing to the prevalence of benzylic carbon stereocenters in natural products and medicinally active compounds.[1] Notwithstanding the magnificent insurgence of transition metal-catalyzed C–H activation chemistry during the past decade,[2] Friedel-Crafts (FC) alkylation[3] remained arguably the most straightforward strategy for the introduction of unfunctionalized alkyl groups into (hetero)arenes (Scheme 1A).[4]

Over the years, a plethora of catalytic methods have been instituted for achieving enantioselective FC reactions.[5] An overwhelming majority of these reactions relied on the use of substrates bearing electrophilic sp^2 carbon center.[5] In addition to being prochiral, the presence of functional groups in these substrates eases their activation and enantiofacial discrimination (Scheme 1B). In contrast, the application of electrophiles, containing reactive sp^3 carbon center, in enantioselective FC reactions has been scarce.[6] Such racemic electrophilic substrates necessitate the intervention of either a dynamic kinetic resolution (DKR) or a dynamic kinetic asymmetric transformation (DyKAT) pathway to avoid the use of overstoichiometric amount of electrophile.[7] For reactions proceeding via a prochiral intermediate (e.g., carbocation), discrimination between the two enantiotopic faces becomes an enormous challenge due to the absence of any functional group (Scheme 1B).[8]

Transition metal-catalyzed allylic[9-11] and allenylic alkylations[11a] are transformations which make use of electrophiles bearing sp^3 carbon at the reaction center. Several inter- and intramolecular enantioselective FC allylic alkylation reactions have been developed under Pd[12] and Ir-catalysis,[13] which paves the way for the formal introduction of unfunctionalized 3-carbon alkyl chains into (hetero)arenes, with the generation of benzylic carbon stereocenters (Scheme 1B). The closely related FC allenylic alkylation reactions, on the other hand, remained largely unexplored.

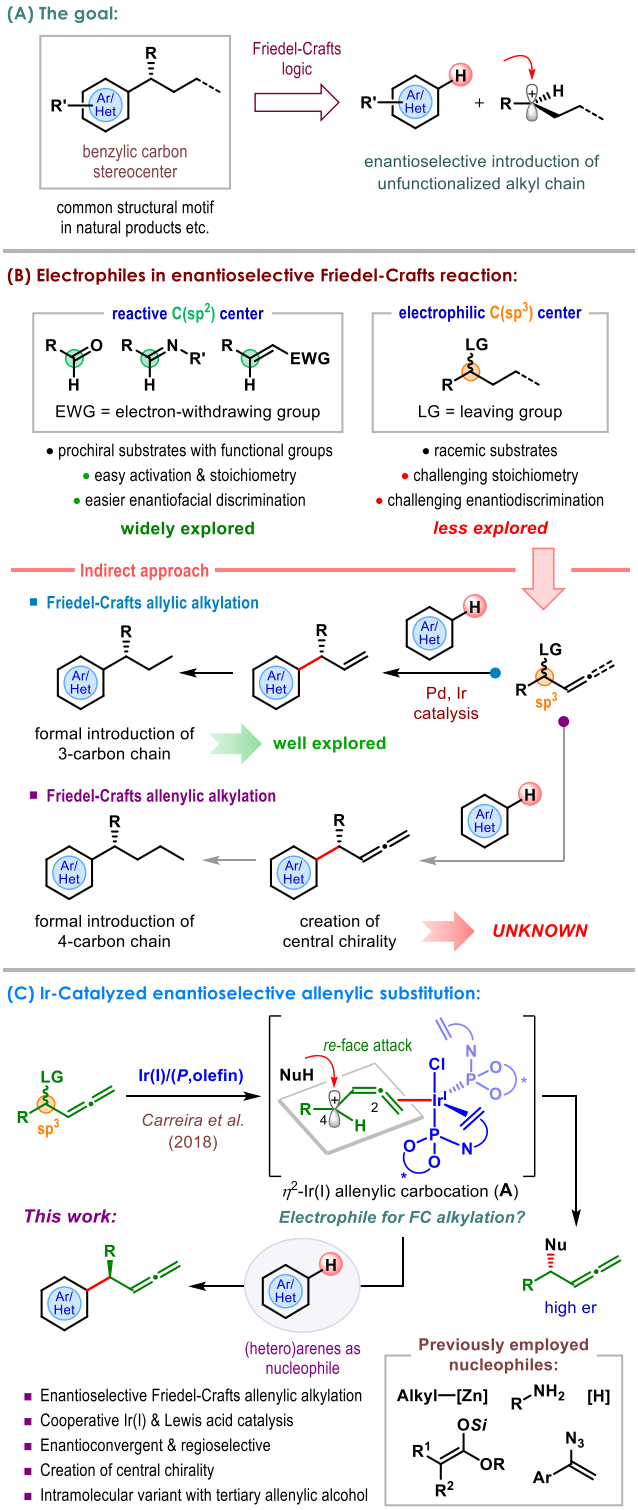
During the course of this study, a report by Yu, Shao and co-workers described a Pd-catalyzed FC allenylic alkylation of indoles for the enantioselective synthesis of axially chiral allenes.[14] However, enantioselective FC allenylic alkylation for the creation of central chirality is yet to be developed.

Iridium-catalyzed enantioselective allenylic substitution reaction, introduced by Carreira et al. in 2018,[15] is mechanistically distinct from its more widely explored palladium-catalyzed variants.[16-17] Unlike the involvement of η^3-Pd(II)-butadienyl intermediates in Pd(0)-catalyzed allenylic substitution,[16-17] the reactions catalyzed by Ir(I)/(phosphoramidite,olefin)-complex[11c] proceed through a η^2-Ir(I) intermediate and don't involve any change in the formal oxidation state of iridium (Scheme 1C).[15] More importantly, this η^2-Ir(I) intermediate **A** is shown to be carbocationic in nature,[15] which makes it a potential candidate for FC reaction. However, (hetero)arenes are a class of nucleophiles, which has never been employed in this reaction. As such, only a few nucleophiles have so far been explored in this Ir-catalyzed enantioselective allenylic alkylation reaction, namely alkylzinc reagents,[15] ammonia surrogates,[18] hydride (from Hantzsch ester),[19] silyl ketene acetals[20] and vinyl azides[21] (Scheme 1C).

As a part of our ongoing research program dedicated to the development of enantioselective C(sp^2)–H allylic[22] and allenylic alkylation reactions, we decided to employ (hetero)arenes as nucleophile in Ir-catalyzed allenylic alkylation reaction. However, (hetero)arenes are less reactive compared to the previously utilized nucleophiles[15,18-21] in this reaction (see above). Nonetheless, we reasoned that the η^2-Ir(I)-bound allenylic carbocation would be sufficiently electrophilic to be intercepted

by suitably substituted electron-rich (hetero)arenes and should facilitate the desired FC reaction. Moreover, the proposed trigonal bipyramidal coordination sphere of Ir(I) bearing two (*P*,olefin) ligands, even though distant from the reaction site, has been shown to offer necessary face-selectivity for nucleophilic addition to the prochiral carbocation in **A** (Scheme 1C).[15,19] Therefore, the same selectivity can be expected in the enantiodetermining C–C bond formation step with (hetero)arenes.

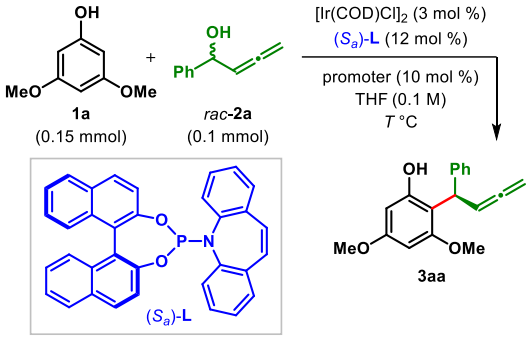
Scheme 1. Enantioselective Friedel-Crafts Allenylic Alkylation: Backdrop of This Study



Apart from enantioselectivity, we were cognizant of two regiochemical issues: While the regioselectivity on the allenylic carbocation **A** has been shown to be reliably dictated in favor of nucleophilic addition at C4 (vs C2) by the ligands on Ir (Scheme 1C),[15] the site selectivity on the (hetero)arenes must be left to their innate reactivity.

Herein we present the results of this investigation, which culminated in the first Ir-catalyzed enantioselective Friedel-Crafts allenylic alkylation (Scheme 1C).

Table 1. Optimization of Reaction Conditions for Enantioselective FC Allenylic Alkylation[a]



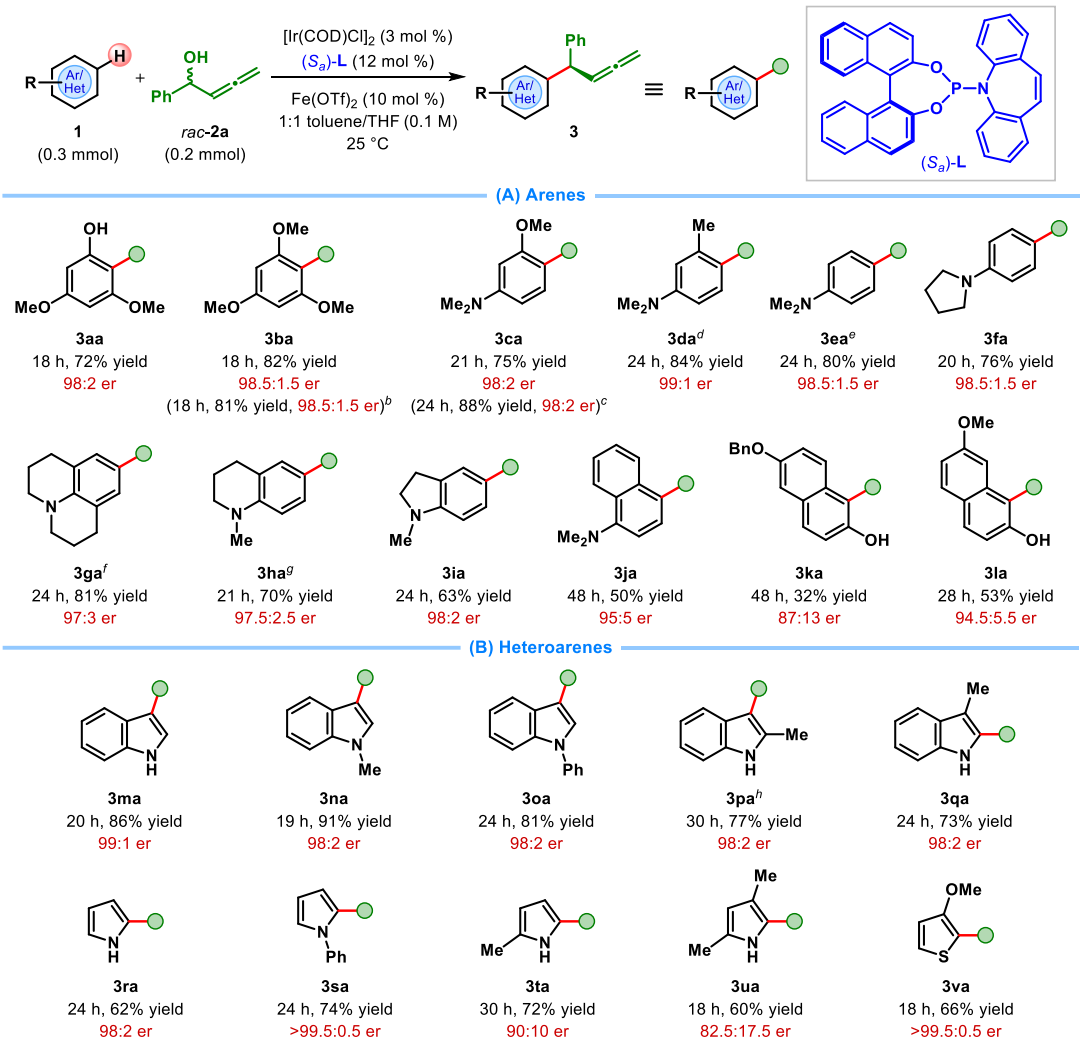
entry	promoter	*T* (°C)	*t* (h)	yield (%)[b]	er[c]
1	$Sc(OTf)_3$	50	3	38	78:22
2	$Bi(OTf)_3$	50	3	<5	n.d.
3	$Fe(OTf)_2$	50	3	(54)	97.5:2.5
4	$Zn(OTf)_2$	50	3	55	98:2
5	$Yb(OTf)_3$	50	3	(55)	96:4
6	$La(OTf)_3$	50	3	58 (52)	98:2
7	$BF_3{\cdot}OEt_2$	50	3	29	81:19
8	CSA	50	3	55	93:7
9[d]	$Fe(OTf)_2$	50	3	53	85:15
10[e]	$Fe(OTf)_2$	50	3	77 (73)	95.5:4.5
11[e]	$Fe(OTf)_2$	25	18	77	95:5
12[f]	$Fe(OTf)_2$	25	18	(71)	98:2
13[f]	$La(OTf)_3$	25	24	59 (54)	82:18

[a]Unless noted otherwise, reactions were carried out on a 0.1 mmol scale. [b]Yields were determined by ^{1}H NMR analysis with mesitylene as internal standard. Isolated yield is given in parentheses. [c]Enantiomeric ratios (er) were determined by HPLC analysis on a chiral stationary phase. [d]Reaction in CH_2Cl_2. [e]Reaction in toluene. [f]Reaction in 1:1 toluene/THF. CSA = camphorsulfonic acid. n.d. = not determined.

At the outset of our study, FC allenylic alkylation of 3,5-dimethoxyphenol **1a** with racemic allenylic alcohol *rac*-**2a** in the presence of 6 mol % of a catalyst derived from $[Ir(COD)Cl]_2$ and Carreira's (*P*,olefin) ligand (S_a)-**L**[11c] was selected as the model reaction (Table 1). The reason behind this choice of substrate was twofold. While the electron rich nature of **1a** was reasoned to facilitate the FC reaction, we were apprehensive of the possible overalkylation processes. Therefore, it was important to identify reaction conditions which would favor only the monoalkylated product. At the same time, we wanted to verify the regioselectivity of the monoalkylation process (i.e., C2- vs C4-substitution) with an unsymmetrical arene such as **1a**. The reaction with an excess of arene **1a** in THF at 50 °C using $Sc(OTf)_3$ as the Lewis acidic promoter indeed furnished the FC allenylic alkylation product **3aa** (Table 1, entry 1). Despite the low yield and modest enantioselectivity, the formation of only the monosubstituted product with complete regioselectivity in favor of C2 was encouraging and provided the impetus for further investigation. In line with the earlier studies, no diene product, arising from the addition to **A** at its 2-position (Scheme 1C), could be detected. Screening of other Lewis and Brønsted acidic promoters (entries 2-8) revealed $Fe(OTf)_2$ and $La(OTf)_3$ to be nearly equally efficient as **3aa** was isolated with similar levels of yield and er in both these cases (entries 3 and 6). At this

stage, we decided to use $Fe(OTf)_2$ for further optimization. The reaction in toluene was found to be faster but **3aa** was formed with diminished er (entry 10). It is possible to carry out this reaction at room temperature without much influence on the enantioselectivity (entry 11): Although expectedly slower, it makes the process operationally simpler. Combining the effect of toluene in improving the reaction rate and that of THF in enhancing the enantioselectivity led to the identification of a 1:1 mixture of THF and toluene as the optimum reaction medium, when **3aa** was isolated in 71% yield with 98:2 er (entry 12). Under the same reaction conditions, $La(OTf)_3$ delivered **3aa** with much inferior yield and enantioselectivity (entry 13). Efforts to ameliorate the reaction outcome by tweaking other reaction parameters proved unsuccessful.[23]

Scheme 2. Scope of (Hetero)arenes in Enantioselective FC Allenylic Alkylation[a]



[a]Unless noted otherwise, reaction conditions indicated above were followed. Yields correspond to the isolated yield after chromatographic purification. Enantiomeric ratios (er) were determined by HPLC analysis using a stationary phase chiral column. [b]Reaction on a 1.0 mmol scale. [c]Reaction using 1.0 mmol of **1c** and 1.2 mmol of *rac*-**2a** under 4 mol % of $Ir[(S_a)\text{-}\mathbf{L}]_2Cl$. [d]Reaction using 0.5 mmol of **1d** and 0.75 mmol of *rac*-**2a** under 4 mol % of $Ir[(S_a)\text{-}\mathbf{L}]_2Cl$. [e]Reaction using 0.4 mmol of **1d** and 0.6 mmol of *rac*-**2a**. [f]Reaction using 0.4 mmol of **1g** and 0.6 mmol of *rac*-**2a**. [g]Reaction using 0.5 mmol of **1h** and 0.75 mmol of *rac*-**2a**. [h]Reaction using 0.24 mmol of *rac*-**2a** and 0.2 mmol of **1p**.

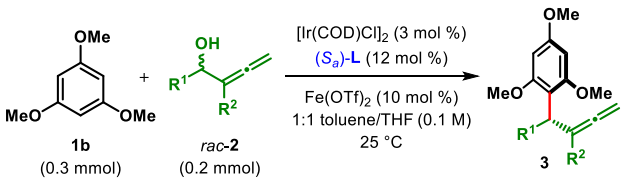
The catalyst, promoter and the reaction conditions optimized for the FC allenylic alkylation of 3,5-dimethoxyphenol **1a** (Table 1, entry 12) was then extended to other arenes and heteroarenes for reaction with racemic allenylic alcohol *rac*-**2a** (Scheme 2). We were delighted to find that our protocol is not restricted to electron-rich phenols such as **1a**. Structurally and electronically related arenes such as 1,3,5-trimethoxybenzene **1b** and 3-methoxy-*N*,*N*-dimethylaniline **1c** fared equally well

under our reaction conditions and afforded allenylic arenes **3ba** and **3ca**, respectively, with similar level of yields and enantioselectivities (Scheme 2A). In the latter case, FC allenylic alkylation took place exclusively at C4. The presence of hydroxy or methoxy group on the arene ring is not a prerequisite for this reaction. Replacing the methoxy group in **1c** with a less electron-releasing methyl doesn't appear to affect the reactivity of **1d**, as the regioselective C4 product **3da** was isolated in 84% yield and with 99:1 er. In fact, FC allenylic alkylation of *N*,*N*-dimethylaniline (**1e**) and other analogous *N*,*N*-dialkylaniline derivatives (**1f**-**i**) themselves was found to occur efficiently and selectively at the *para*-position of the *N*,*N*-dialkylamine substituent in moderate to good yield with good to excellent enantioselectivity. Naphthalene derivatives (**1j**-**l**), adorned with electron-rich substituents, are viable substrates for this FC allenylic alkylation reaction. However, these reactions turned out to be much less efficient and enantioselective. Unfortunately, electronically lesser endowed arenes such as phenol, toluene, anisole and naphthol (both α- and β-) failed to react under our optimized conditions.[23]

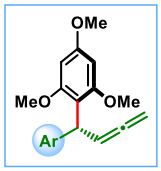
In the realm of heteroarenes, indole (**1m**) as well as *N*-protected indoles (**1n**-**o**) served as excellent substrates and furnished C3-allenylic indoles **3ma**-**oa** in very high yield with superb enantioselectivity (Scheme 2B). The reaction with 2-methylindole (**1p**), although somewhat sluggish, was equally enantioselective. In the case of 3-methylindole (**1q**), C2-allenylic alkylation product **3qa** was formed in 73% yield with 98:2 er. Whether this reaction proceeds by direct C2-alkylation or via initial C3-alkylation of indole followed by rearrangement, could not be confirmed at this stage. Pyrrole (**1r**) and its derivatives (**1s**-**u**) showed fairly good reactivities, even though enantioselectivities varied depending on the nature and the position of the substituents. While pyrrole (**1r**) itself and *N*-phenylpyrrole (**1s**) afforded the C2-allenylic alkylation products **3ra** and **3sa**, respectively, with excellent enantioselectivities, the reactions of 2-methylpyrrole (**1t**) and particularly 2,4-dimethylpyrrole (**1u**) took place with significantly reduced enantioselectivity. 3-Methoxythiophene **1v**, on the other hand, turned out to be a good substrate and delivered C2-allenylic thiophene derivative **3va** with an outstanding er of >99.5:0.5. Among other heteroarenes tested, (benzo)furans, carbazoles and *N*-methylimidazole were found to be unsuitable substrates for FC allenylic alkylation under our optimized protocol.[23]

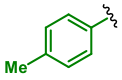
For showcasing the scope of allenylic alcohols, 1,3,5-trimethoxybenzene **1b** was chosen as the nucleophile. The examples compiled in Scheme 3A indicate the generality of this enantioselective FC allenylic alkylation protocol with respect to racemic allenylic alcohols bearing aryl substituents. Electronically diverse substituents on various positions of the aryl ring were well tolerated and furnished the desired products generally in high yield and with excellent enantioselectivity. Of specific note is the FC product **3bk**, bearing a boronate functionality, which could be subjected to diversification through various cross coupling reactions. The enantiopurity of the 1-bromonaphthyl-substituted product **3bp** could be further improved after a single crystallization. Single crystal X-ray diffraction analysis of crystals thus obtained for **3bp** established its absolute configuration to be (*S*) (CCDC 2302758, Scheme 3A). Configuration of the other FC allenylic alkylation products shown in this report were assigned in analogy with **3bp**.

Scheme 3. Scope of Allenylic Alcohols in Enantioselective FC Allenylic Alkylation[a]

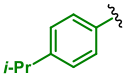


(A) Aryl

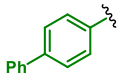




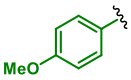
3bb
18 h, 87% yield
98.5:1.5 er



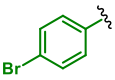
3bc
12 h, 77% yield
97:3 er



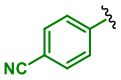
3bd
14 h, 85% yield
98:2 er



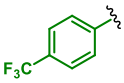
3be
18 h, 83% yield
96:4 er



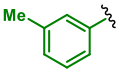
3bf
18 h, 83% yield
96:4 er



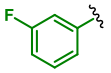
3bg
18 h, 78% yield
98:2 er



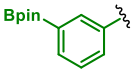
3bh
28 h, 69% yield
99:1 er



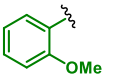
3bi
18 h, 85% yield
99:1 er



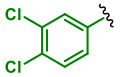
3bj
18 h, 83% yield
99:1 er



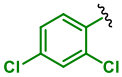
3bk
18 h, 56% yield
98:2 er



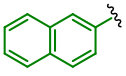
3bl
18 h, 70% yield
96:4 er



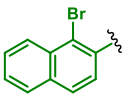
3bm
18 h, 73% yield
n.d.[b]



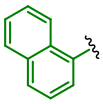
3bn
18 h, 78% yield
99:1 er



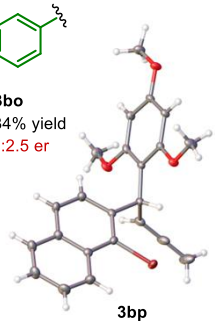
3bo
18 h, 84% yield
97.5:2.5 er



3bp
18 h, 71% yield
98.5:1.5 er (99.8:0.2 er)[c]

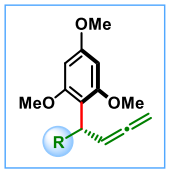


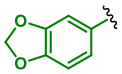
3bq
18 h, 84% yield
98:2 er



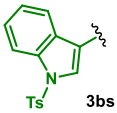
3bp
(CCDC 2302758)

(B) Others

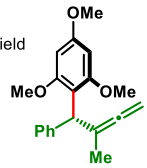




3br
18 h, 88% yield
97:3 er



3bs
16 h, 75% yield
91:9 er



3bt[d]
14 h, 47% yield
89:11 er

3bu
18 h, 74% yield
97.5:2.5 er

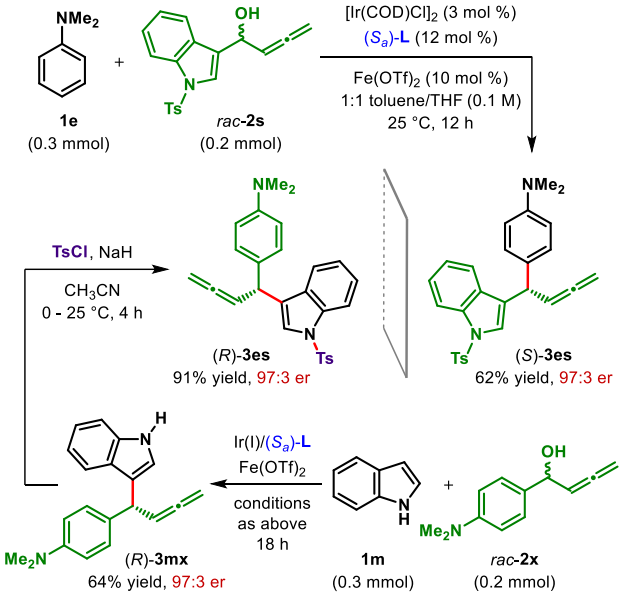
3bv[e]
19 h, 88% yield
82:18 er

3bw[f]
14 h, 70% yield
85:15 er

[a]Unless noted otherwise, reaction conditions indicated above were followed. Yields correspond to the isolated yield after chromatographic purification. Enantiomeric ratios (er) were determined by HPLC analysis using a stationary phase chiral column. [b]n.d. = er could not be determined with the available chiral columns. [c]The numbers in the parentheses indicate er after a single recrystallization. [d]Reaction using 0.2 mmol of **1b** and 0.3 mmol of *rac*-**2t**. [e]Reaction using 0.2 mmol of **1b** and 0.3 mmol of *rac*-**2v**. [f]Reaction at 50 °C.

Apart from aryl substituents as shown in Scheme 3A, allenylic alcohols, containing heterocyclic substituents such as dioxolane, indole, furan and thiophene, could also be utilized as allenylic electrophile for FC reaction with **1b** (Scheme 3B). However, most of these reactions proved to be relatively less enantioselective compared to their aryl counterparts. While most aliphatic allenylic alcohols failed to react under our optimized conditions,[23] cyclopropyl-substituted allenylic alcohol **2v** displayed substantial reactivity and furnished the desired product **3bv** in 88% yield, albeit with only modest enantioselectivity.

Scheme 4. Substrate-Controlled Enantiodivergent Synthesis of Diarylallenylic Methane **3es**

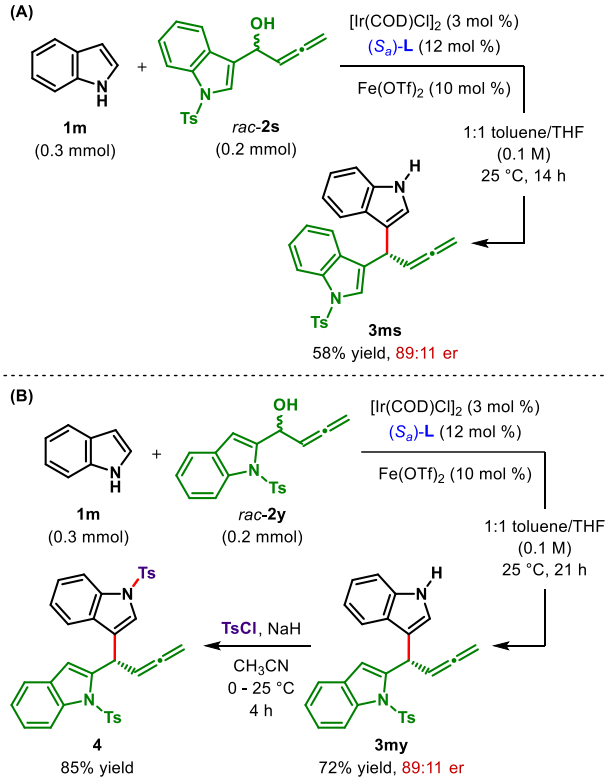


In the Ir-catalyzed enantioselective allenylic substitution reactions reported till date, allenylic alcohols or their derivatives bearing monosubstituted allene unit have most commonly been employed as allenylic electrophile. Reactions with allenylic alcohols having disubstituted allene have been shown to be less efficient and considerably less enantioselective.[15,18] We were pleased to find 2,2-disubstituted allenylic alcohol **2w** to be a competent substrate for our FC allenylic alkylation reaction. However, as expected, **2w** was found to be less reactive compared to its monosubstituted analogue **2a**. Accordingly, the reaction needed to be carried out at an elevated temperature (50 °C) and the product (**3bw**) was obtained with moderate er.

Having showcased the broad generality of both the reaction partners in this enantioselective FC allenylic alkylation reaction, we realized the potential of our protocol in providing access to both the product enantiomers under the influence of a single catalyst antipode – simply through the choice of substrates. The implementation of this strategy was demonstrated by substrate-controlled enantiodivergent synthesis of diarylallenylic methane **3es** (Scheme 4). The reaction of *N*,*N*-dimethylaniline **1e** with *N*-tosyl-3-indolyl substituted allenylic alcohol **2s** under our standard conditions using (S_a)-(*P*,olefin) ligand (S_a)-**L** afforded (*S*)-**3es** in 62% yield with 97:3 er. On the other hand, when indole (**1m**) was employed as the nucleophile for reaction with *N*,*N*-dimethylaniline-substituted allenylic alcohol **2x** under the same catalytic conditions, (*R*)-**3mx** was obtained in 64% yield with 97:3 er. *N*-Tosylation of indole in (*R*)-**3mx** resulted in (*R*)-**3es** with complete conservation of stereochemical integrity.

Our protocol also provides a platform for the enantioselective synthesis of chiral allenylic methane derivatives bearing two very similar substituents at the stereocenter. For example, FC allenylic alkylation of indole (**1m**) with *N*-tosyl-3-indolyl substituted allenylic alcohol (**2s**) delivered bis(indolyl)allenylic methane **3ms** with 89:11 er (Scheme 5A). Stereogenicity of **3ms** arises due to the *N*-protection of one of the indole moieties. Similarly, reaction of indole (**1m**) with *N*-tosyl-2-indolyl substituted allenylic alcohol (**2y**) furnished another bis(indolyl)allenylic methane **3my** with 89:11 er (Scheme 5B). *N*-Tosylation of **3my** generated **4**, which is chiral due to different connectivity of the indole rings (C2 and C3) with the stereocenter. Enantioselective synthesis of both **3ms** and **4** can be difficult by other means.

Scheme 5. Enantioselective Syntheses of Bis(indolyl)allenylic Methanes

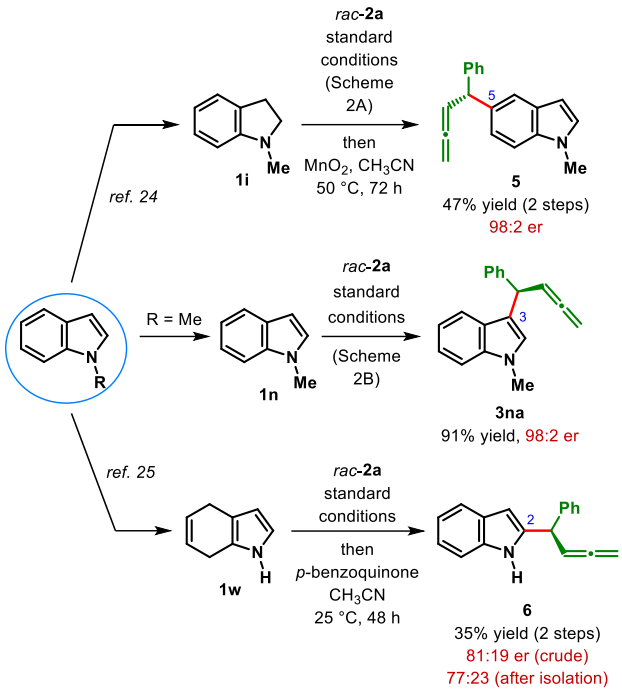


As shown in Scheme 2, indoles (**1m**-**o**) and indoline (**1i**) display different regioselectivity in this FC reaction. This innate reactivity pattern of indole and its derivatives was exploited for the regiodivergent allenylic alkylation of indoles (Scheme 6). While direct FC reaction of *N*-methylindole (**1n**) led to C3-allenylic alkylation product **3na**, a two-step protocol consisting of FC allenylic alkylation of *N*-methylindoline (**1i**)[24] followed by oxidation with MnO_2[13b] resulted in C5-allenylic alkylation product **5** in 47% overall yield with 98:2 er. Similarly, starting from 4,7-dihydro-1*H*-indole (**1w**), FC allenylic alkylation and oxidative aromatization with *p*-benzoquinone[25] furnished C2-allenylic indole **6**. Unfortunately, **6** was found to be sensitive to silica gel and also configurationally labile.

Apart from the 1.0 mmol scale reactions depicted for **3ba** and **3ca** in Scheme 2, this enantioselective FC allenylic alkylation reaction can be further scaled up with lower catalyst loading. As exemplified for the reaction between **1a** and *rac*-**2a** in the presence of 4 mol % *in situ* generated Ir[(*S*$_a$)-**L**]$_2$Cl, both the catalytic activity as well as the yield and enantioselectivity were retained even with a 20-fold increase in the scale of the reaction (Scheme 7A).

The allene moiety in FC allenylic alkylation products can act as a linchpin for synthetic elaboration to other building blocks, especially in cooperation with functionalities at the *ortho*-position of the arene ring. Molybdenum-catalyzed hydrosilylation of allene in **3ba** proved to be highly regio- and diastereoselective and resulted in (*Z*)-allylsilane **7** in 61% yield (Scheme 7B).[26] Rhodium-catalyzed intramolecular hydroalkoxylation of **3aa** gave dihydrobenzofuran derivative **8** exclusively as the *cis*-isomer in 84% yield.[27] The corresponding *trans*-dihydrobenzofuran **9** can be obtained under gold-catalysis,[28] but with considerably less dr. Organocatalytic intramolecular iodoetherification[29] of **3aa** worked reasonably well under bifunctional tertiary aminothiourea ***epi*-QD-TU** to give 2-iodovinyl dihydrobenzofuran derivative **10**, albeit with only 2.2:1 dr.

Scheme 6. Regiodivergent Allenylic Alkylation of Indoles

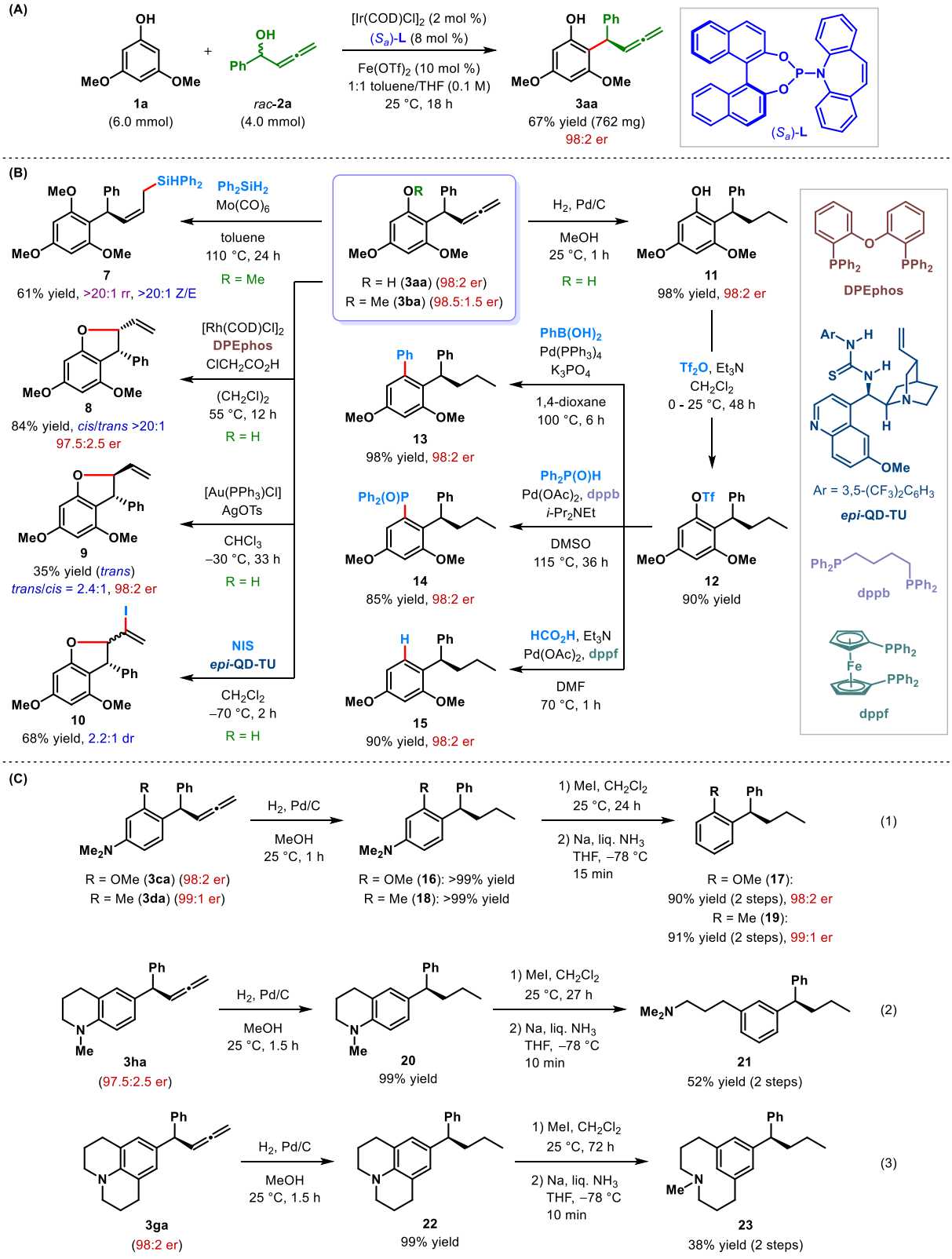


Hydrogenation of the allene functionality allows for the formal introduction of unfunctionalized 4-carbon alkyl chain into an (hetero)arene ring with the creation of a benzylic carbon stereocenter as shown for the conversion of **3aa** to **11** (Scheme 7B). The presence of the hydroxy group in **11** provides a handle for the installation of other functional groups on the arene ring through the intermediacy of the corresponding triflate **12**. For instance, Pd-catalyzed Suzuki coupling of **12** with phenyl boronic acid gave biaryl derivative **13** in excellent yield. Another Pd-catalyzed coupling with diphenylphosphine oxide led to **14** through the formation of a C–P bond. The triflate group in **12** can also be removed under Pd-catalyzed hydrogenolytic conditions using triethylammonium formate[30] to furnish the formal FC alkylation product of 1,3-dimethoxybenzene **15** – directly inaccessible via FC allenylic alkylation reaction due to low nucleophilicity of 1,3-dimethoxybenzene.

The use of *N*,*N*-dialkylaniline derivatives as nucleophile in the FC allenylic alkylation reaction is equally advantageous for accessing such less electron-rich arene derived formal FC alkylation products. Cleavage of the dialkylamino substituents from arenes is possible following the two-step protocol developed by MacMillan et al.[31] Thus, FC allenylic alkylation products **3ca** and **3da** could be transformed into formal FC alkylation products of anisole (**17**) and toluene (**19**), respectively, in excellent yield (Scheme 7C, eq 1). This synthetic maneuver not only allowed for the access of FC alkylation products of inherently inert nucleophiles such as toluene and anisole in the Ir-catalyzed FC allenylic alkylation reaction (*vide supra*), but also ensures '*ortho*-selectivity' in the products **17** and **19**.

The exposure of *N*-methyl tetrahydroquinoline-derived FC allenylic alkylation product **3ha** to the same reaction conditions resulted in the rupture of the tetrahydroquinoline ring to form **21** (Scheme 7C, eq 2), which represents a facile and enantioselective route to '*meta*-selective' formal FC alkylation products through the utilization of cyclic *N*,*N*-dialkylaniline derivatives as nucleophile. Starting from the tricyclic substrate **3ga**, the same synthetic manipulation led to *meta*,*meta*-disubstituted formal FC alkylation product **23**, with the concomitant formation of a 10-membered macrocycle (Scheme 7C, eq 3).

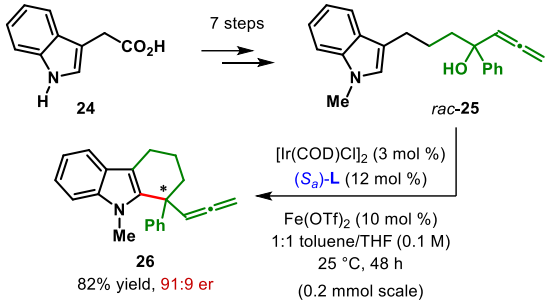
Scheme 7. Scale-up of Enantioselective FC Allenylic Alkylation Reaction and Synthetic Elaboration of Products



Despite notable progress in the area of asymmetric allenylic substitution reactions under Pd and Ir-catalysis, there has been no report on their intramolecular variants.[32] After exploring the scope and limitations of this Ir-catalyzed enantioselective FC

allenylic alkylation reaction, we wondered about the viability of the same catalyst system for an intramolecular variant. For this purpose, indole-tethered racemic tertiary allenylic alcohol *rac*-**25** was synthesized from commercially available indole-3-acetic acid **24** (Scheme 8). When subjected to our standard reaction conditions, *rac*-**25** underwent facile intramolecular FC reaction to furnish tetrahydrocarbazole derivative **26**, bearing an all-carbon quaternary stereogenic center, in 82% yield and with 91:9 er. This is the first example of an enantioselective intramolecular allenylic alkylation reaction. Moreover, this reaction also revealed the possibility of using tertiary allenylic alcohols as substrate in Friedel-Crafts reaction.

Scheme 8. Ir-Catalyzed Enantioselective Intramolecular Friedel-Crafts Allenylic Alkylation



In conclusion, (hetero)arenes were employed for the first time as nucleophile in Ir-catalyzed allenylic substitution reaction and led to the development of the first catalytic enantioselective Friedel-Crafts allenylic alkylation for creating central chirality. Using easily accessible racemic allenylic alcohol as the electrophile, this reaction is catalyzed by a cooperative combination of a Ir(I)-bis(phosphoramidite,olefin) complex and Lewis acidic $Fe(OTf)_2$ and proceeds in an enantioconvergent fashion to deliver 1,1-disubstituted allenylic methanes, generally with good to excellent enantioselectivity. This reaction is completely regioselective in favor of allenes over 1,3-dienes. Hydrogenation of the allene functionality in the products allows for the enantioselective formal introduction of 4-carbon alkanes into (hetero)arenes with the creation of a benzylic stereocenter. While the FC reaction displays complete regiocontrol with respect to (hetero)arenes, it is possible to synthesize a few other regioisomeric products through the judicious choice of (hetero)arene derivatives, post-synthetic modification or by removal of functional groups on the (hetero)arene ring. Preliminary experiments established the feasibility of an enantioselective intramolecular FC allenylic alkylation as well as the viability of using tertiary allenylic alcohols as substrate in FC reaction under the same catalytic conditions. The latter finding is particularly exciting as it would lead to enantioselective construction of a diaryl-containing all-carbon-quaternary center. Further exploration in these directions is ongoing in our laboratory.

Acknowledgment

We gratefully acknowledge financial support from the Science and Engineering Research Board (SERB) in the form of the Science and Technology Award for Research (SERB-STAR) [Grant No. STR/2021/000009] and a Core Research Grant [Grant No. CRG/2020/000176]. P. D. thanks the Ministry of Education, Government of India for his doctoral fellowship through the Prime Minister's Research Fellowship (PMRF) scheme. D. G. thanks Indian Institute of Science, Bangalore for his fellowship. We thank Mr. Kishorkumar Sindogi (Central X-Ray Facility, IISc Bangalore) for his assistance with single crystal X-ray diffraction analysis. Our special thanks are due to Professor Dattatraya H. Dethe (Department of Chemistry, Indian Institute of Technology, Kanpur) for a gift of the compound **1w**. High resolution mass spectra (HR-MS) were recorded on equipment procured under the Department of Science and Technology (DST)-FIST grant [Grant No. SR/FST/CS II-040/2015].

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