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Iron-Catalyzed *Ortho*-Allylation of Aromatic Carboxamides with Allyl Ethers

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Supporting Information

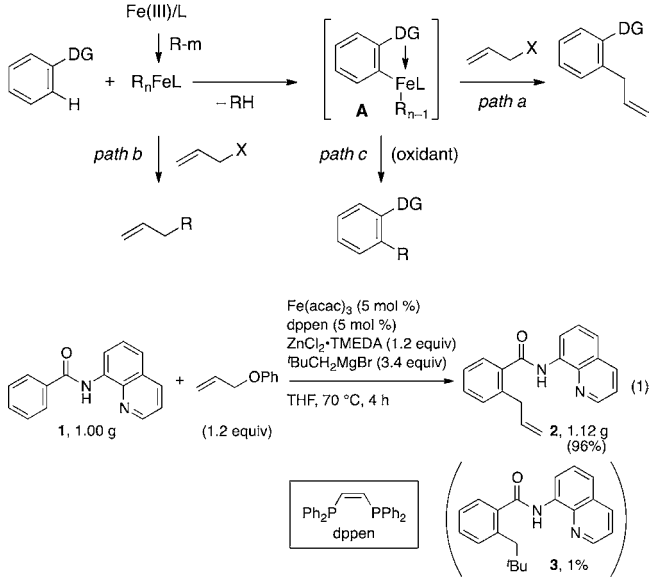
ABSTRACT: Arenes possessing an *N*-(quinolin-8-yl)-amide directing group are *ortho*-allylated with allyl phenyl ether in the presence of an iron/diphosphine catalyst and an organometallic base at 50−70 °C. The reaction proceeds via fast iron-catalyzed C−H activation, followed by reaction of the resulting iron intermediate with the allyl ether in γ-selective fashion.

Derivatives of allylbenzene, a partial structure of natural products and bioactive compounds,[1] which serve as versatile intermediates in synthesis, are typically synthesized via the reaction of an aryl donor with an allylic fragment.[2] Allylation of arenes under classical Friedel−Crafts conditions[3] is straightforward but often limited to electron-rich arenes, and a mixture of regioisomers and over-allylated products is often produced. Significant advances in transition-metal-catalyzed C−H allylation have been made,[4−8] among which the recent Rh-catalyzed mild allylation reactions reported by Glorius,[5d] Ma,[6b] and Cramer[6c] are particularly attractive. Upon exploring the synthetic potential of iron catalysis,[9] we found that allylation of benzamide and congeners can be achieved in high yield under mild conditions without the need for precious metals.[10] We report here an iron-catalyzed *ortho*-allylation of *N*-(quinolin-8-yl)carboxamide derivatives with an allyl ether[11] that occurs in a γ-selective manner with respect to the allylic leaving group. In this reaction, a putative chelated iron intermediate couples with a carbon electrophile, as opposed to previous reports in which it was coupled with a nucleophile under oxidative conditions.[12]

During the course of our previous studies on iron catalysis, we made a serendipitous observation that a chelated intermediate **A** (Scheme 1) that formed after C−H bond cleavage[12d,13] reacts with an allyl ether[14] via path a, instead of the standard cross-coupling reaction of R with an allyl group[15] (path b) or the oxidative C−C bond formation (path c) that we have extensively explored.[12] We suppressed the latter reactions by choosing the quinolin-8-yl group on the amide moiety, *t*-$BuCH_2MgBr$ as the organometallic reagent that acts as a base, and *cis*-1,2-bis(diphenylphosphino)ethylene (dppen) as a ligand. Use of the (quinolin-8-yl)amide group has recently been shown to be beneficial for C−H bond activation reactions.[12g,16]

We commenced our investigation with the iron-catalyzed activation of the *o*-C−H bond in various directing-group-possessing arenes,[12] followed by reaction with allyl phenyl ether. We found that a substrate bearing a bidentate directing group, *N*-(quinolin-8-yl)benzamide (**1**), selectively affords the

Scheme 1. Reaction Design and Competing Pathways for Iron-Catalyzed Directed C−H Activation Followed by Reaction with an Allyl Electrophile



allylation product (path a), while the competing reactions (paths b and c) are suppressed. Thus, **1** (1.00 g, 4.03 mmol) reacted with allyl phenyl ether (1.2 equiv) in the presence of $Fe(acac)_3$ (5 mol %), dppen (5 mol %), $ZnCl_2$·TMEDA (1.2 equiv, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine), and *t*-$BuCH_2MgBr$ (3.4 equiv) to afford the *ortho*-allylated product in 96% yield after 4 h at 70 °C (eq 1). Under these conditions, *ortho*-neopentylated product **3** (path c) was obtained in a trace amount (1%), and 0.15 equiv of allyl ether was recovered. Reaction with 1.0 equiv of allyl phenyl ether afforded **2** in 89% yield. We noted that 3.4 equiv of *t*-$BuCH_2MgBr$ is necessary: 1 equiv is consumed to deprotonate the amide proton, and the other 2.4 equiv forms 1.2 equiv of $(t\text{-}BuCH_2)_2Zn$. Use of the corresponding monoalkylzinc halide instead of $(t\text{-}BuCH_2)_2Zn$ greatly decreased the yield. Besides the directing group, the organometallic base, the diphosphine ligand, and the allylating reagent are important for controlling the reactivity and product selectivity. Thus, when organozinc reagents such as Ph_2Zn or Me_2Zn were used instead of the neopentyl reagent, **2** was obtained in a trace amount, and paths b and c were dominant. In the absence of a ligand, or in the presence of a bipyridine-

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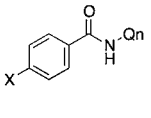
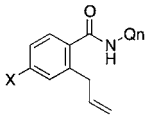
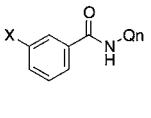
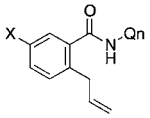
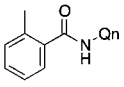
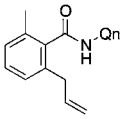
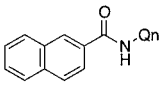
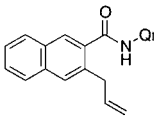
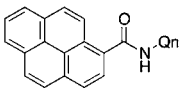
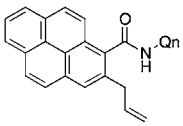
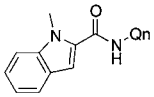
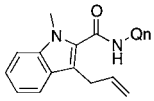
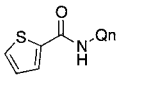
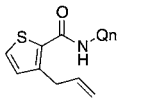
type ligand, a monodentate phosphine, or diphosphines having a flexible backbone (dppe), the substrate was largely recovered. 1,2-Bis(diphenylphosphino)benzene (dppbz) and congeners performed well; dppen showed the best performance (Supporting Information (SI)). We notice that the use of this ligand for catalysis has been largely ignored to date. Allylic substrates possessing a better leaving group, such as allyl chloride, acetate, and carbonate, were less effective (SI).

The scope of the allylation reaction is illustrated in Table 1. The reaction with carboxamides bearing an electron-donating

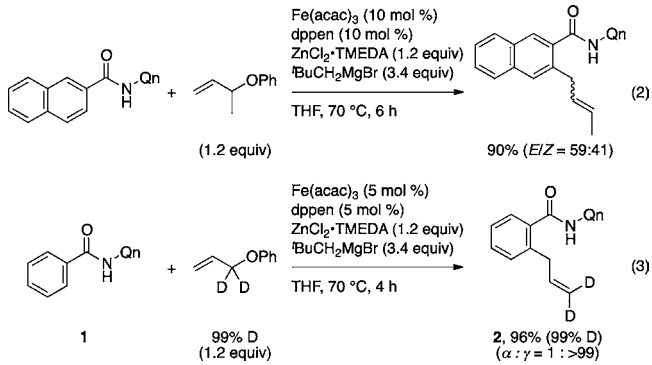
Table 1. Iron-Catalyzed Allylation of *N*-(Quinolin-8-yl)benzamides with Allyl Phenyl Ether[a]

entry	substrate	product	time (h)	yield (%)
1[b]			4	96 (X = H)
2			4	97 (X = Me)
3			4	96 (X = OMe)
4[c,d,f,h]			24	93 (X = F)
5			15	93 (X = Cl)
6[c,d,f,h]			24	92 (X = Br)
7			36	90 (X = CF_3)
8			6	74 (X = CO_2Me)
9			4	95 (X = Me)
10			4	98 (X = OMe)
11[e,g,h]			160	74
12			4	98
13[e,g,i]			135	68
14			18	91
15[c]			40	61

[a]The reaction was performed under the conditions in eq 1 on a 0.4 mmol scale. Qn = quinolin-8-yl. [b]1 g scale. [c]50 °C. [d]10 mol % catalyst. [e]20 mol % catalyst. [f]1.5 equiv of $ZnCl_2$·TMEDA and 4.0 equiv of *t*-$BuCH_2MgBr$. [g]2.0 equiv of $ZnCl_2$·TMEDA and 5.0 equiv of *t*-$BuCH_2MgBr$. [h]1.5 equiv of allylOPh. [i]2.0 equiv of allylOPh.

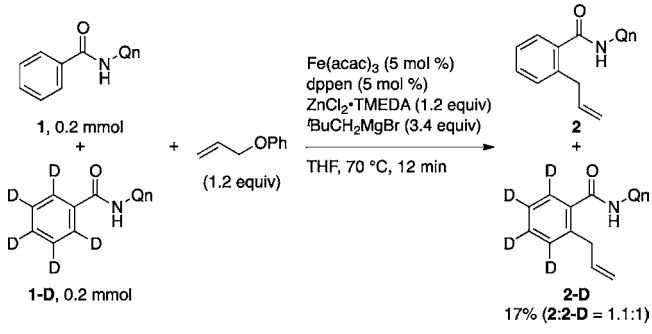
or electron-withdrawing substituent at the *para* position proceeded smoothly to afford the corresponding *ortho*-allylated product in good yields, though the latter needed longer reaction times (entries 1–8). Functional groups such as chloride, bromide, trifluoromethyl, and ester are tolerated. *Meta*-substituted carboxamides reacted smoothly at the less hindered *ortho* position (entries 9 and 10). Allylation of *ortho*-substituted substrate (entry 11) on the opposite *ortho* position proceeded slowly but still in good yield if higher catalyst loading and longer reaction time were employed. This slow reaction accounts for the selective mono-allylation. The C–H bond of naphthalene, pyrene, and heteroarenes such as indole and thiophene could also be allylated in a regioselective manner (entries 12–15). We did not find any isomeric styrene compound, despite the reports on double bond isomerization of terminal olefins in the presence of an iron catalyst and an organometallic reagent.[17]

The reaction with allyl phenyl ether possessing a methyl group at the α position afforded only the γ product in high yield but as a mixture of stereoisomers (*E*/*Z* = 59:41) (eq 2). The *E*/*Z* ratio remained constant throughout the reaction (SI), indicating that the stereo mixture is due not to product isomerizaton but to the allylation step itself. Attempts to control the *E*/*Z* ratio using ligands with different electronic and steric properties resulted in little change in the ratio. Allyl phenyl ethers possessing a substituent at the β or γ position did not participate in the reaction. The reaction of (1,1-dideuterioallyloxy)benzene selectively afforded the γ product in 96% yield, which confirmed the preferred γ-selective allylation (eq 3).



An intermolecular competitive reaction in which an equimolar amount of **1** and **1-D** was used was stopped at 17% conversion to give an intermolecular kinetic isotope effect (KIE) value of 1.1 (Scheme 2). The observed low KIE value

Scheme 2. Intermolecular KIE Experiment



suggests that the C–H bond cleavage step is not involved in the turnover-limiting step, unlike in the iron-catalyzed oxidative C–H bond arylation reaction, which showed a high KIE value.[12d,g] The intermediacy of a metallic species such as **A** in Scheme 1 was confirmed by D_2O quenching of the reaction of **1** with 1 equiv of iron/diphosphine in the absence of allyl phenyl ether. The degree of deuterium incorporation was proportional to the

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amount of iron/diphosphine used (1 equiv, 88% D; 0.75 equiv, 73% D; 0.5 equiv, 45% D, 0 equiv, 0% D; see Table S6), strongly suggesting that **A** is a species containing an iron atom. Reaction of preformed **A** with allyl phenyl ether gave **2** in 54% yield (SI).

In conclusion, we have found that iron-catalyzed directed *ortho*-allylation proceeds smoothly to afford allylbenzene derivatives with high γ selectivity and without isomerization of the double bond to styrene derivatives. The reaction demonstrates, for the first time, that iron-catalyzed directed C–H bond activation could be utilized for coupling with an electrophile. Further studies on iron-catalyzed coupling of C–H bonds with electrophiles are ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and physical properties of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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