JOC The Journal of Organic Chemistry

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Diasteroselective and Enantioselective Ir-Catalyzed Allylic Substitutions of 1-Substituted 1-Fluoro-1-(arenesulfonyl)methylene Derivatives

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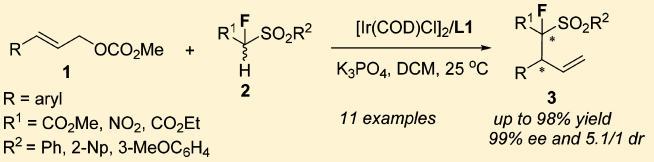
Supporting Information

ABSTRACT: diasteroselective and enantioselective Ir-catalyzed allylic substitutions of 1-substituted 1-fluoro-1-(arenesulfonyl)methylene derivatives are presented, which afford the fluorinated allyl products with two chirality centers. The steric demand of 1-substituted 1-fluoro-1-(arenesulfonyl)-methylene derivatives and allylic substrates has a great influence on the *dr* values of these reactions. The transformation of the branched allyl product into the fluorinated 3,4-dihydro-2*H*-pyrrole 1-oxide was discussed, as well.



The enantioselective introduction of a fluorinated methylene group into organic molecules could dramatically enhance their physicochemical and biological properties;[1] for example, popular drugs[2] such as clevudine,[2a,b] clofarabine,[2c] fluticasone furoate,[2d] and difluprednate[2e] contain a chiral carbon-fluorinated carbon fragment (Figure S1). A strategy for the enantioselective incorporation of a fluorinated methylene unit into organic molecules is by transition-metal-catalyzed asymmetric allylic substitution of fluorinated methylene derivatives.[3] In this regard, fluorinated methylene derivatives including fluorobisphenylsulfonylmethane[4] and 2-fluoromalonate[5] were applied in Pd-[6] or Ir[7]-catalyzed asymmetric allylation reactions in which a chiral carbon-fluorinated carbon center was formed. However, racemic fluorinated methylene derivatives, which afford the allyl products with two chiral centers, have been less investigated. Notably, it is challenging to control the stereochemistry of this type of reactions.[8] In addition, the fluorinated allyl products are of great importance for the synthesis of high value-adding compounds.[9] To the best of our knowledge, Ir-catalyzed allylic substitution of racemic fluorinated methylene derivatives is hardly reported. In this paper, we report Ir-catalyzed allylic substitutions of 1-substituted 1-fluoro-1-(arenesulfonyl)-methylene derivatives, which give the allyl products with two chiral centers.

We started our investigation with a reaction of (*E*)-cinnamyl methyl carbonate **1a** with diverse racemic fluorinated methylene derivatives in the presence of an iridacycle[7a,d] made from $[Ir(COD)Cl]_2$ and Feringa's ligand **L1** in DCM at room temperature. After a series of experiments, we found that methyl 2-fluoro-2-(phenylsulfonyl)acetate **2a** gave the allylic product **3a** with increasing dr in comparison with ethyl 2-fluoro-3-oxobutanoate **2e**, which gave the corresponding allyl product with no diasteroselectivity.[8b] As a result, **2a** was employed for further investigation. The nature of bases has a considerable impact on the result of Ir-catalyzed allylic substitution;[7] the subsequent examination of bases such as Cs_2CO_3, CsF, K_2CO_3, and K_3PO_4 revealed that K_3PO_4 gave superior results, 85% yield with 99% ee, b/l 99/1, and dr 4.3/1 (Table 1, entry 4). The other bases provided somewhat lower dr and yields (Table 1, entries 1−3). A solvent survey indicated that the use of DCM offered the highest efficiency, regioselectivity, and enantioselectivity but moderate diastereoselectivity; the use of MeCN and THF gave lower dr and yields but maintained excellent regio- and enantioselectivities (entries 6 and 7). Toluene is not effective for this reaction (entry 5). The other iridium species including $[Ir(Cp^*)Cl]_2$ and $[Ir(dba)_3]$ were also explored, and they are not able to catalyze this reaction (entries 8 and 9). Next, a range of chiral ligands including Feringa's **L1**, **L2**, **L3**, and **L4** were evaluated (Figure 1). The use of **L1** offered the best result (entry 3); **L2**, with two bulky 2-naphthyl groups, gave rise to **3a** in a decreasing yield with high regio- and enantioselectivity but fair diastereoselectivity (entry 4 vs entry 10). **L3**, with a less steric phenyl ring, and **L4**, with a 2-methylpiperidinyl group, failed to promote this reaction, presumably due to their mismatched effect on this reaction (entries 11 and 12). Variation of the reaction temperature has a considerable impact on the efficiency and stereoselectivities of this reaction (entries 4, 13, and 14).

Once we established that the iridacycle[7a,d] catalyzed the diastereo- and enantioselective allylation efficiently, the scope

Received: July 18, 2017
Published: September 6, 2017

DOI: 10.1021/acs.joc.7b01782
J. Org. Chem. 2017, 82, 10693−10698

OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 5383−5386

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Chemoselective, Regioselective, and Enantioselective Allylations of NH_2OH under Iridium Catalysis

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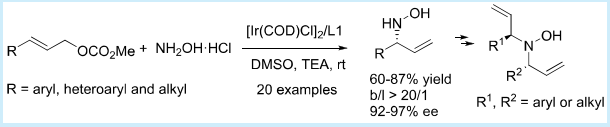
Supporting Information

ABSTRACT: The utilization of unprotected NH_2OH, which is not only an oxygen nucleophile but also a nitrogen nucleophile, in iridium-catalyzed allylic substitution is realized under mild conditions. The chemoselectivity, stereoselectivity, and multiple allylation are controlled by adjusting the reaction conditions. This method produces the *N*-(1-allyl)-hydroxylamines in good to high yields with high level of chemoselectivities, regioselectivities, and enantioselectivities. The application of allylated hydroxylamine (*R*)-**3a** in the synthesis of diallylated hydroxylamine **6** is achieved, along with an excellent diastereomeric ratio.

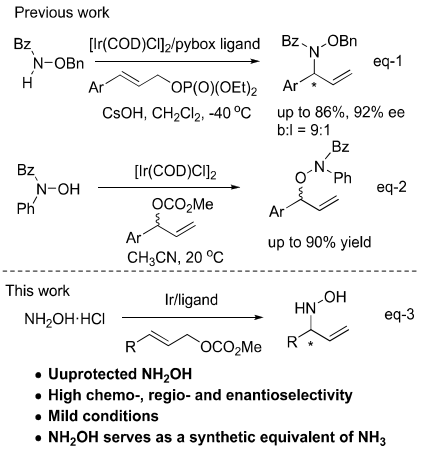


Nitrogen chemistry has been attracting scientists because nitrogen is fundamental to all of life and many industrial processes. The very important nitrogen-containing reagents such as ammonia (NH_3), hydrazine (N_2H_4), and hydroxylamine (NH_2OH) are synthesized from the reaction of N_2, H_2, and O_2 by the Haber−Bosch (H-B) process.[1] NH_2OH is a well-known inorganic reagent; it is inexpensive and abundant in the area of chemistry and chemical industry.[2] Iridium-catalyzed asymmetric allylic substitution has become a powerful tool for the chiral carbon−nitrogen or carbon−oxygen bond formation.[3]

The application of hydroxylamine derivatives in this type of reaction to form C−N bond or C−O bonds was investigated, in which NH_2OH must be protected with Bn or Bz in order to improve the chemoselectivity and to inhibit the multiple allylation (see eq-1 and eq-2 in Scheme 1).[4] There are some drawbacks in these methods: (a) the protected groups should be removed from the N- or O-group after the allylation reaction; and (b) the steric demand of Bn or Bz decreases the regioselectivity and enantioselectivity. The use of NH_2OH[5] in such a reaction, giving the allylated hydroxylamine derivatives, has not been reported until now. The allylated hydroxylamine derivatives are of great importance to [2,3]-sigmatropic rearrangement.[6] Compared to NH_3[7] as a nucleophile, NH_2OH contains either N or O reactive sites. As shown in Scheme 1, a competition between a nitrogen nucleophile and an oxygen nucleophile on NH_2OH will occur; in addition to that, the resulting allylamines,[7] which are more reactive than NH_2OH, will further undergo the allylation reaction.[4] Thus, Ir-catalyzed allylation of NH_2OH remains a challenge. We envision that (a) NH_2OH will occur via Ir-catalyzed allylic substitution and (b) chemoselective allylation will occur (see eq-3 in Scheme 1). In this paper, we described Ir-catalyzed allylic substitutions of NH_2OH.

To explore the hypothesis, we began with a reaction of (*E*)-cinnamyl methyl carbonate (**1a**) with NH_2OH·HCl (**2**) in the presence of an iridacycle[8] made from $[Ir(COD)Cl]_2$ and Feringa's ligand (**L1**)[9,10] (Figure 1). A solvent survey indicated that dimethyl sulfoxide (DMSO) is a suitable solvent (see Table 1, entry 1), while other solvents such as dichloromethane (DCM), acetonitrile, and ethanol gave **3a** in poor yields with **3a**/**3a**′ > 20/1 (see Table 1, entries 2, 4, 6, and 7); tetrahydrofuran (THF), dimethyl formamide (DMF), and toluene are not effective for this reaction (Table 1, entries 3, 5, and 6). After screening a range of bases, **1a**/**2** ratios, and temperatures (see the Supporting Information), when the reaction of **1a** (0.1 mmol) with **2** (0.2 mmol) in Et_3N and DMSO at room temperature was performed, the formation of

Scheme 1. Hydroxylamines Employed in Ir-Catalyzed Allylic Substitution



Received: April 17, 2019
Published: May 22, 2019

DOI: 10.1021/acs.orglett.9b01357
Org. Lett. 2019, 21, 5383−5386