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Catalytic Selenium-Promoted Intermolecular Friedel–Crafts Alkylation with Simple Alkenes

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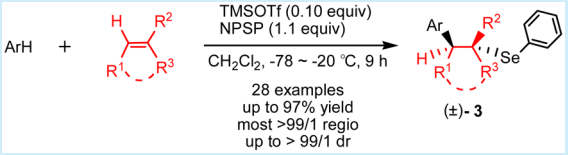
Supporting Information

ABSTRACT: A method for conducting selenium-promoted intermolecular Friedel–Crafts (F–C) alkylation reactions has been developed with simple alkenes using trimethylsilyl trifluoromethanesulfonate as a catalyst and *N*-phenylselenophthalimide as an efficient selenium source. Electron-rich arenes smoothly underwent F–C alkylation with a variety of alkenes to afford alkylated products in good yield and with high regioselectivity and diastereoselectivity. The regioselectivity and stereoselectivity of arenes and alkenes as well as a preliminary mechanism of the F–C alkylation reaction are discussed.



As an important cornerstone of chemistry, Friedel–Crafts (F–C) alkylation provides a powerful method for forming new carbon–carbon bonds and has been widely utilized in contexts ranging from academic experiments to industrial processes.[1] The stereoselective version of this reaction with alkenes has attracted considerable interest and has been enhanced by significant recent progress.[2] Despite considerable effort, most successful examples of these processes have focused on relatively reactive aromatic compounds such as furans, pyrroles, and indoles with activated alkenes[3] via 1,4-conjugate addition[4] or with intermediate compounds derived from alkenes, such as epoxides,[5] and three-membered ring halonium ions generated by a ring-opening reaction.[6] Therefore, there is an urgent requirement to develop novel stereoselective F–C reactions, particularly for undeveloped arenes such as benzene derivatives with simple alkenes.

Organoselenium compounds are potentially bioactive and can be used as valuable synthetic intermediates.[7,8] Similarly to halonium ions, a three-membered ring seleniranium ion[9] is attacked by external carbon-centered nucleophiles such as alkenyl silyl ethers, trimethylsilyl cyanide, allyltrimethylsilane, and aromatic compounds to afford different carboselenenylation products of alkenes with good *trans* stereospecificity.[10] Although the utility of electrophilic selenium reagents for carbon–heteroatom bond-formation reactions has been well documented, the potency of electrophilic organoselenium reagents for carbon–carbon bond-formation reactions has been examined relatively infrequently.[11] With the exception of indoles,[12] aromatic compounds such as furan, thiophene, *N*-methylpyrrole, azulene, and a few electron-rich benzene derivatives have been used to afford the products of selenium-promoted intermolecular F–C alkylation of alkenes in low yields. Furthermore, the key three-membered cyclic episelenonium ion intermediate was derived from the strongly electrophilic areneselenenyl trifluoromethanesulfonate via addition to olefins or from an alcohol bearing a phenylseleno group on the adjacent carbon atom via an acid-induced reaction.[10] However, the aforementioned F–C alkylation is uneconomical because they use large quantities (specifically 5–10 times the quantity of selenides) of alkenes, aromatic compounds, and Lewis acids. Yoshida treated alkenes with benzenenselenenyl arenesulfonate and anisole in acetonitrile or nitromethane to give anisylselenenylated compounds in low to high yields. However, 46 equiv of anisole was used in the anisylselenenylation reaction.[10e] Here, we report an economical, efficient, trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyzed and weak electrophilic selenium-promoted intermolecular F–C alkylation with alkenes that could provide an alternative method for synthesizing 1,1-diaryl-2-phenylselenoalkanes in good yields and with high regioselectivity and stereoselectivity. Moreover, the resulting alkylated arenes containing α-seleno functionality could provide a further avenue for structural elaboration.

A current interest in our laboratory is the Lewis acid catalyzed selenofunctionalization of olefins.[13] Inspired by the Brønsted acid catalyzed carboselenenylation of styrenes with indole[12] and Lewis acid mediated carboannulation,[14] we found that Lewis acids and Brønsted acids could activate weak electrophilic organoselenides, such as *N*-phenylselenosuccinimide (NPSS) and *N*-phenylselenophthalimide (NPSP), and facilitate the formation of episelenonium ions from olefins. Recently, we have described TMSOTf-catalyzed and polymer-supported NPSS-promoted intramolecular F–C alkylation with tethered alkenes for the synthesis of annulated aromatic heterocycles.[15] Fortunately, only 0.10 equiv of TMSOTf was used in our intramolecular F–C alkylation reactions (Scheme 1),[16] whereas 2.10 equiv of TMSOTf was used in the reported carboannulation.[14] Accordingly, we anticipated that a suitable Lewis acid might catalyze the selenium-promoted intermolecular F–C alkylation of arenes with alkenes. To achieve this objective, we screened different Lewis acids as catalysts for the selenium-

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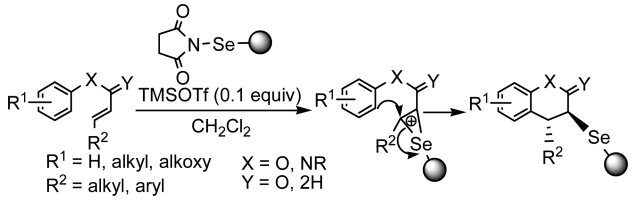
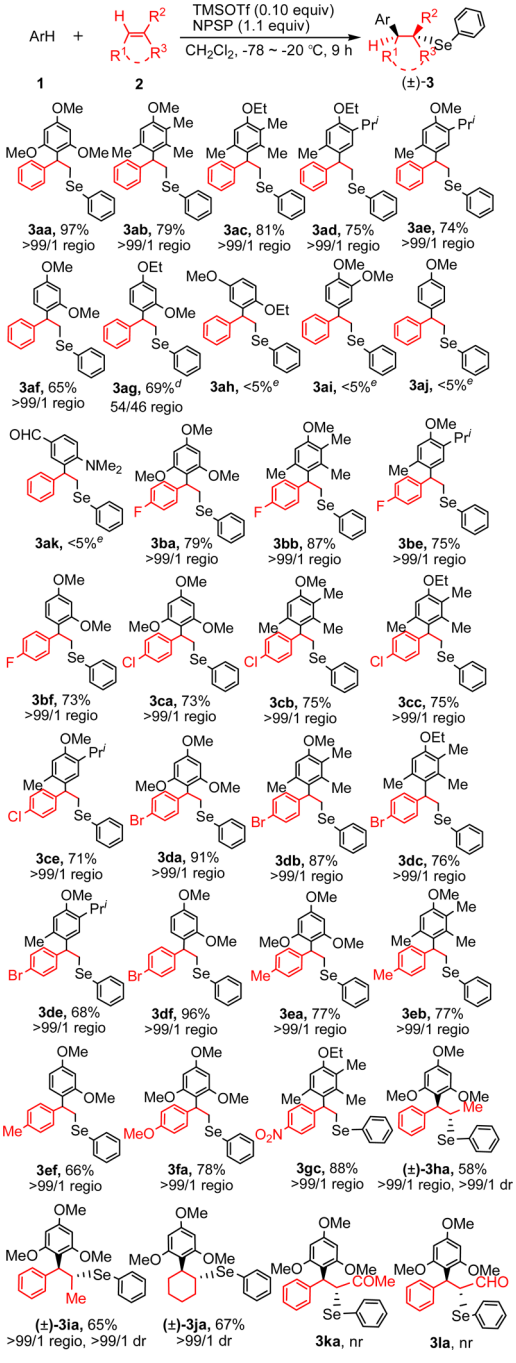
Scheme 1. Selenium-Promoted Intramolecular F−C Alkylation with Tethered Alkenes



promoted F−C alkylation of 1,3,5-trimethoxy benzene (**1a**) with styrene (**2a**), using NPSP as the selenium source, and optimized the reaction conditions. In the absence of a Lewis acid catalyst, the reaction afforded no F−C-alkylated product. In addition, $TiCl_4$, $AlCl_3$, $FeCl_3$, $ZnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$, AgOTf, and $Sm(OTf)_3$ did not exhibit catalytic activity. TMSOTf was found to be the best catalyst, resulting in an isolated yield of product **3aa** of up to 97%. The optimized F−C alkylation reaction conditions are 0.10 equiv of TMSOTf, 1.0 equiv of alkenes, 1.0 equiv of arenes, and 1.1 equiv of NPSP in CH_2Cl_2 at −78 °C for 2 h and then at −20 °C for 7 h.

With the optimized conditions established, we then expanded the substrate scope; the results are indicated in Scheme 2. In general, the tested reactions all proceeded smoothly to afford products in moderate to good yields and with high regioselectivity. In particular, good yields and 99% regioselectivity were achieved with styrene and styrene bearing electron-withdrawing nitro, chloro, fluoro, and bromo substituents and electron-donating methyl and methoxy substituents (Scheme 2, **3aa−f,ba−f,ca−e,da−f,ea−f,fa,gc**). In contrast, the F−C alkylation reaction was rather sluggish when electron-deficient olefins such as *α,β*-unsaturated carbonyl compounds were used as the substrate (Scheme 2, **3ka,la**). Moreover, simple cyclic alkenes such as cyclohexene reacted smoothly to generate products with high diastereoselectivity (Scheme 2 and Figure 1, **3ja**). (*Z*)- and (*E*)-*β*-methylstyrenes afforded products in good yields and with 99% regioselectivity and diastereoselectivity (Scheme 2, **3h−ia**). In addition, benzene bearing more than two electron-donating substituents and *m*-dialkoxybenzenes produced good results (Scheme 2, **3aa−g,ba−f,ca−e,da−f,ea−f,fa,gc,h−ja**), whereas *ortho*- and *para*-disubstituted benzenes, monosubstituted benzenes, and benzenes bearing electron-withdrawing substituents such as formyl afforded yields of less than 5% (Scheme 2, **3ah−k**) and instead generated hydroxyselenenylation products and small quantities of amidoselenenylated products and diaryl selenides because the F−C alkylation reactions were quenched with a saturated aqueous solution of $NaHCO_3$ and phthalimide counteranion has poor nucleophilicity; these results indicate that the F−C alkylation reaction occurred more readily if more electron-donating substituents were present in the benzene ring. For unsymmetrical substituted benzenes, the combined effects of the carbon nucleophile and steric hindrance in the benzene ring governed the regioselectivity of the substituted benzenes in the F−C alkylation reaction; trisubstituted benzenes, tetrasubstituted benzenes, and symmetrical *meta*-disubstituted benzenes afforded the products with high regioselectivity (Scheme 2, **3ab−f,bb,3be−f,cb−e,db−f,eb−f,gc,kb−c**), whereas unsymmetrical *meta*-disubstituted benzenes, such as 1-ethoxy-2-methoxybenzene, afforded products with low regioselectivity (Scheme 2, **3ag**). In addition, Markovnikov-type adducts with good yields derived from the highly regioselective carboselenenylation of styrenes and *trans*-

Scheme 2. Scope of Intermolecular Selenium-Promoted F−C Alkylation with Alkenes[a−c]



[a]The general reaction was performed on a 0.5 mmol scale in 5 mL of CH_2Cl_2 with a **1**/**2** molar ratio of 1/1; products from **3aa** to **3gc** were produced from styrene (**2a**) and substituted styrene (**2b−g**); products **3h−ja** were produced, respectively, from (*E*)-*β*-methylstyrene (**2h**), (*Z*)-*β*-methylstyrene (**2i**), and cyclohexene (**2j**). [b]Isolated yield. [c]The value of dr was determined by ^{1}H NMR. [d]Combined yield of 4-ethoxy-2-methoxy-1-[1-phenyl-2-(phenylseleno)ethyl]benzene (**3ag**) and 2-ethoxy-4-methoxy-1-[1-phenyl-2-(phenylseleno)ethyl]benzene (**3ag′**). [e]The reaction generated hydroxyselenenylation products and a small quantity of diaryl selenides.

type adducts were obtained regioselectively and diastereoselectively via the carboselenenylation of *β*-methylstyrenes and cyclic alkenes. According to the ROESY spectrum of **5ha** and the

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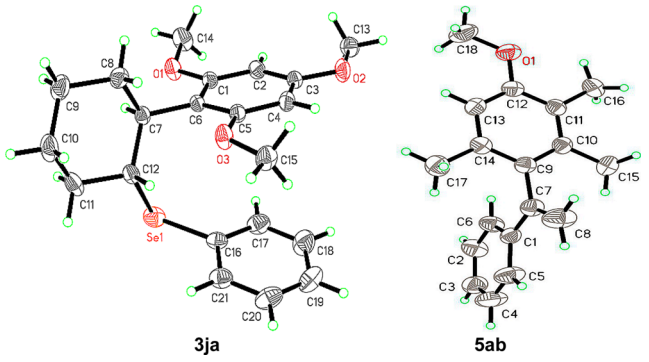
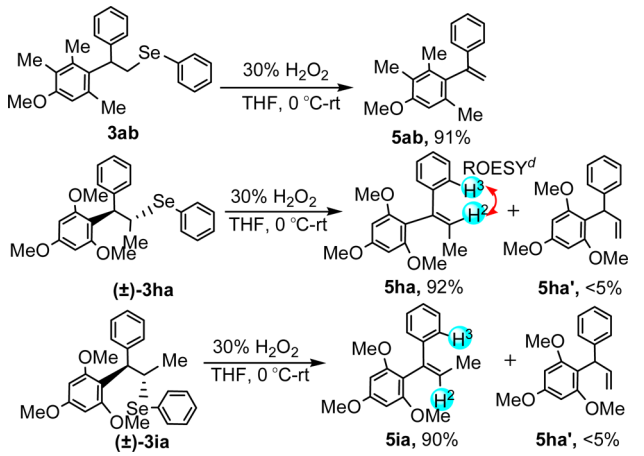


Figure 1. ORTEP structures of compounds **3ja** and **5ab**.

correlation of δ_H (7.24) and δ_H (6.34), together with the ^1H NMR and ^{13}C NMR spectra, the following structure of compound **5ha** can be deduced as (*Z*)-1-(1-phenyl-1-propenyl)-2,4,6-trimethoxybenzene. Therefore, the alkene **5ha** was synthesized from (*E*)-*β*-methylstyphene (**2h**) via *anti*-addition with NPSP and *syn*-elimination of selenoxide (Scheme 3),

Scheme 3. Selenoxide *Syn* Elimination of Compound 3ab[a–c]

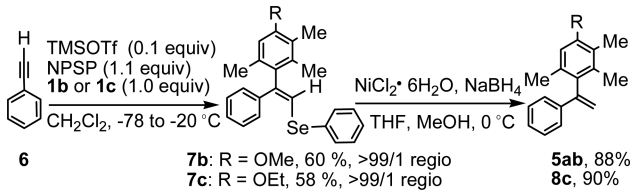


[a]The general reaction was performed on a 0.2 mmol scale in 8 mL of THF and 0.5 mL of H_2O_2 aqueous solution. [b]Isolated yield. [c]ORTEP of the molecular structure of compound **5ab**. [d]The correlation of δH^3 (7.24) and δH^2 (6.34) in the ROESY spectrum of **5ha**.

whereas the alkene **5ia** was obtained from (*Z*)-*β*-methylstyphene (**2i**) via *anti*-addition with NPSP and *syn*-elimination of selenoxide because of no correlation of δ_H (7.25) and δ_H (5.69) in the ROESY spectrum of **5ia** (Scheme 3).

Therefore, the F−C alkylation reaction of (*E*)-*β*-methylstyphene (**2h**) produces (1*S*,2*S*) and (1*R*,2*R*) adducts (±)-**3ha**, and the reaction of (*Z*)-*β*-methylstyphene (**2i**) produces (1*S*,2*R*) and (1*R*,2*S*) adducts (±)-**3ia**. The regioselectivity of the products of the carboselenenylation of alkenes was verified by treating compounds **3ab** with 30% H_2O_2 aqueous solution in THF at 0 °C for 1.5 h and then at room temperature for 30 min to afford **5ab** in 91% yield via a selenoxide *syn*-elimination reaction, and the regioselectivity of the F−C alkylation reaction of 1-methoxy-2,3,5-trimethylbenzene (**1b**) with styrene was established by X-ray analysis of **5ab** (Figure 1). Subsequently, the reaction was investigated using phenylacetylene **6** as a substrate, which afforded *β*-(phenylseleno)styrene **7** in moderate yields and with high regioselectivity. This product was verified via hydride reduction and deselenenylation with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ (Scheme 4).

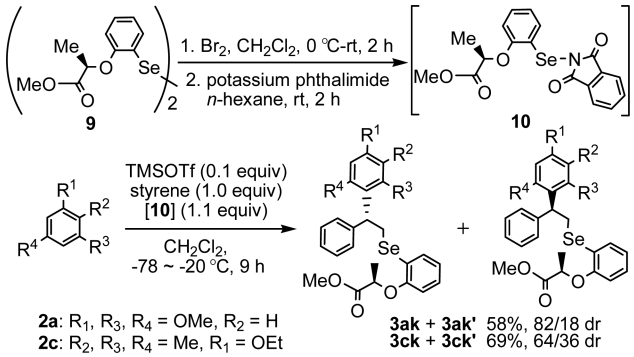
Scheme 4. Synthesis of (*E*)-*α*-(4-Alkoxy-2,3,6-trimethylphenyl)-*β*-(phenylseleno)styrene (7) from Phenylacetylene[a,b] and the Hydride Reduction and Deselenenylation Reaction of Compound 7[b,c]



[a]The general reaction was performed on a 0.5 mmol scale in 5 mL of CH_2Cl_2 for 9 h. [b]Isolated yield. [c]The general reaction was performed on a 0.2 mmol scale in 2 mL of CH_2Cl_2 and 2 mL of THF at 0 °C, with a 7/$NaBH_4$/$NiCl_2{\cdot}6H_2O$ molar ratio of 1/6.8/2.3.

In addition, chiral NPSP **10**, which was synthesized in situ from chiral diaryl diselenide **9**,[16] was used in the F−C alkylation reaction of styrene and 1,3,5-trimethoxybenzene (**1a**) and 1-ethoxy-2,3,5-trimethylbenzene (**1c**) to afford the corresponding carboselenenylation products in good yields and with moderate diastereoselectivity (Scheme 5).

Scheme 5. Synthesis of Chiral NPSP 10 and Intermolecular Chiral Selenium-Promoted F−C Alkylation with Alkenes[a–d]



[a]The reaction was performed on a 0.55 mmol scale in 5 mL of CH_2Cl_2 and with a **9**/Br_2 molar ratio of 11/12. [b]The reaction was performed on a 1.1 mmol scale in 5 mL of hexane and with a selenium bromide/phthalimide potassium molar ratio of 1/1. [c]The reaction was performed on a 1.0 mmol scale in 10 mL of CH_2Cl_2. [d]Isolated yield.

Mechanistically, it appears that TMSOTf activates NPSP by chelating to the amide carbonyl group to facilitate the formation of the episelenonium ion intermediate **12** from alkenes; the subsequent reaction with arenes led to the formation of F−C-alkylated products **3** and the regeneration of the TMSOTf catalyst. Thus, a plausible mechanism has been proposed for the F−C alkylation reaction (Scheme 6). In this scenario, the byproduct phthalimide **15** was found and the silyl enol ether intermediate **13** was verified by ReactIR spectra revealing the stretching vibrational absorption of the O−Si bond at 1033 cm^{-1} (Figure 2).

In conclusion, we have developed a catalytic, efficient, intermolecular F−C alkylation reaction with simple alkenes and arenes that uses NPSP as a selenium source. The intermolecular carbon−carbon bond-forming reaction proceeds

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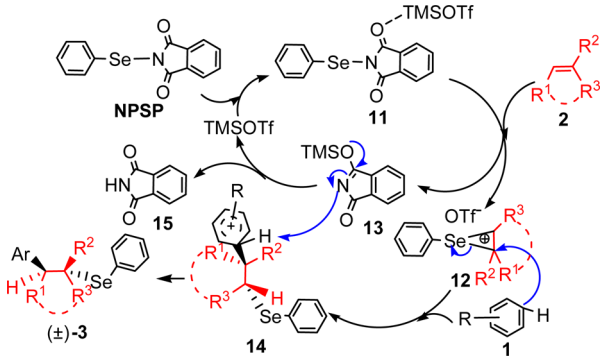
Scheme 6. Mechanistic Hypothesis for the Intermolecular NPSP-Promoted F−C Alkylation Reaction with Alkenes



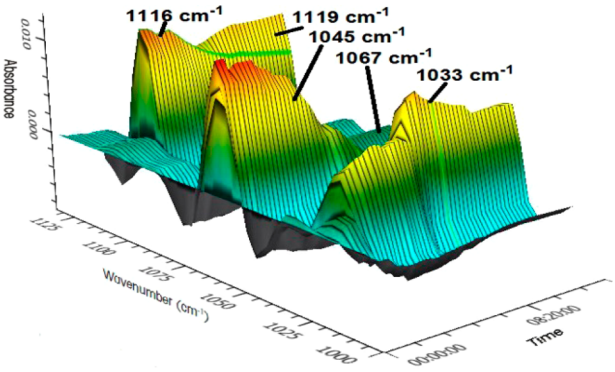


Figure 2. ReactIR spectrum of the F−C alkylation reaction of compound **1b** with styrene and NPSP: 1-methoxy-2,3,5-trimethylbenzene (1b), (υC−O−C) 1116 cm^{-1}; **15**, 1067 cm^{-1}; **3ab**, (υC−O−C) 1119 cm^{-1}; NPSP, 1045 cm^{-1}; **13**, (υSi−O) 1033 cm^{-1}.

with high regioselectivity and diastereoselectivity. This reaction is a convenient procedure for the preparation of 1,1-diaryl-substituted alkenes via selenoxide *syn* elimination and chiral hydrocarbons that bear an aryl moiety at the stereogenic carbon atom if a chiral selenium reagent is used. Efforts to study the asymmetric F−C alkylation reaction using chiral selenium reagents are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03579.

Table presenting the optimization of selenium-promoted F−C alkylation with styrene, experimental procedures, ^{1}H NMR and ^{13}C NMR spectral data for compounds **3**, **5**, **7**, **8**, and **18**, and 2D NMR spectral data for compounds **3ae**, **5ha**, and **5ia** (PDF)

X-ray data for compound **3ja** (CIF)

X-ray data for compound **5ab** (CIF)

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Author Contributions

§Y.Z. and W.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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