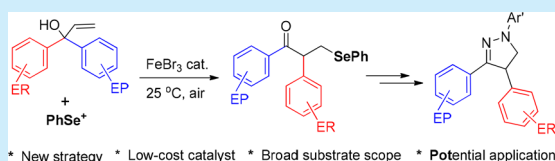


Iron-Promoted Difunctionalization of Alkenes by Phenylselenylation/
1,2-Aryl MigrationPing Wu,^{†,‡,§} Kaikai Wu,^{†,§} Liandi Wang,^{†,§} and Zhengkun Yu^{*,†,§}[†]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, P. R. China[‡]University of Chinese Academy of Sciences, Beijing 100049, P. R. China[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China

S Supporting Information

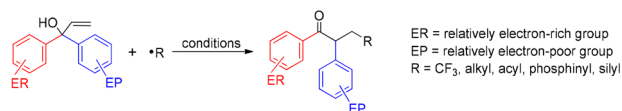
ABSTRACT: Iron-promoted difunctionalization of α,α -diaryl and α -aryl- α -alkyl allylic alcohols has been efficiently achieved by means of *N*-(phenylseleno)phthalimide (N-PSP) under mild conditions. An *in situ* generated phenylselenium cation (PhSe⁺) was added to the olefinic C=C bond to initiate the regioselective phenylselenylation with concomitant 1,2-aryl migration, following a migration preference contrary to the well-known radical pathway. Hydrazonation of the resultant alkene difunctionalization products, that is, α -aryl- β -phenylselenenyl ketones, and subsequent copper-catalyzed dehydroselenylation efficiently afforded functionalized 2-pyrazoline derivatives.



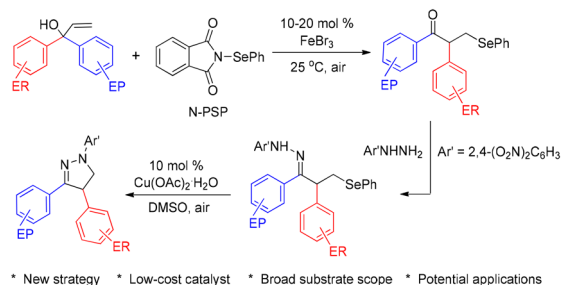
Vicinal difunctionalization of alkenes has been used as a high atom and step-efficiency strategy to simultaneously introduce two functional groups to saturate an olefinic carbon-carbon double bond in organic synthesis.^{1,2} In this context, transition-metal-catalyzed difunctionalization of functionalized allylic alcohols has recently been paid much attention. Cu(I)-catalyzed trifluoromethylation of α,α -diaryl allylic alcohols with concomitant radical 1,2-aryl migration was realized to form β -trifluoromethyl- α -aryl ketones.^{3a} The same strategy was applied for the establishment of α -quaternary carbonyl structures from the tandem trifluoromethylation/semipinacol rearrangement of allylic alcohols.^{3b} An Fe(II)-catalyzed radical procedure was also used for the same purpose.^{3c} In these cases, trifluoromethyl radical addition to the olefinic C=C bond initiated the tandem reactions. Under oxidative conditions, such reactions can also occur. Cu(II) salt-catalyzed cyanomethylation of allylic alcohols with alkyl nitriles was achieved with oxidative radical 1,2-aryl migration.^{4a} Ni(0)-catalyzed oxidative α -C(sp³)-H functionalization of *N,N*-dialkyl-substituted amides with α,α -diaryl allylic alcohols underwent a similar pathway.^{4b} Pd(0)-catalyzed cross-coupling of α -bromocarbonyls with allylic alcohols formed α -aryl-dicarbonyls via the acyl radical intermediates.^{4c} Metal-free oxidative radical 1,2-alkylarylation of α,α -diaryl allylic alcohols was also realized by functionalization of the C(sp³)-H bonds in alkanes,^{4d,e} acetonitriles,^{4e,f} simple ethers,^{4g} alkyl ketones, and analogs.^{4h} Ag(I)-mediated radical phosphinylation/1,2-arylation of α,α -diaryl allylic alcohols was reported.^{5a} A tandem oxidative radical silylation and 1,2-aryl migration was reported for α,α -diaryl allylic alcohols under Cu(I) catalysis, yielding β -silyl ketones.^{5b} Visible-light photoredox catalysis has also been documented for the radical 1,2-alkylarylation^{4d,6a,b} and acylarylation^{6c} of allylic alcohols. For the radical difunctionalization of α,α -diaryl allylic alcohols, a radical is initially added to the olefinic

Scheme 1. Difunctionalization of Allylic Alcohols

(a) Previous work: radical pathway



(b) This work: cation pathway



C=C bond, and then the relatively electron-deficient α -aryl group with lower aromaticity preferentially migrates (Scheme 1a). It is noted that distal 1,*n*-cyano,^{7a} heteroaryl,^{7b} and alkenyl^{7c} migrations have recently been reported in unactivated alkenes by Zhu's group.

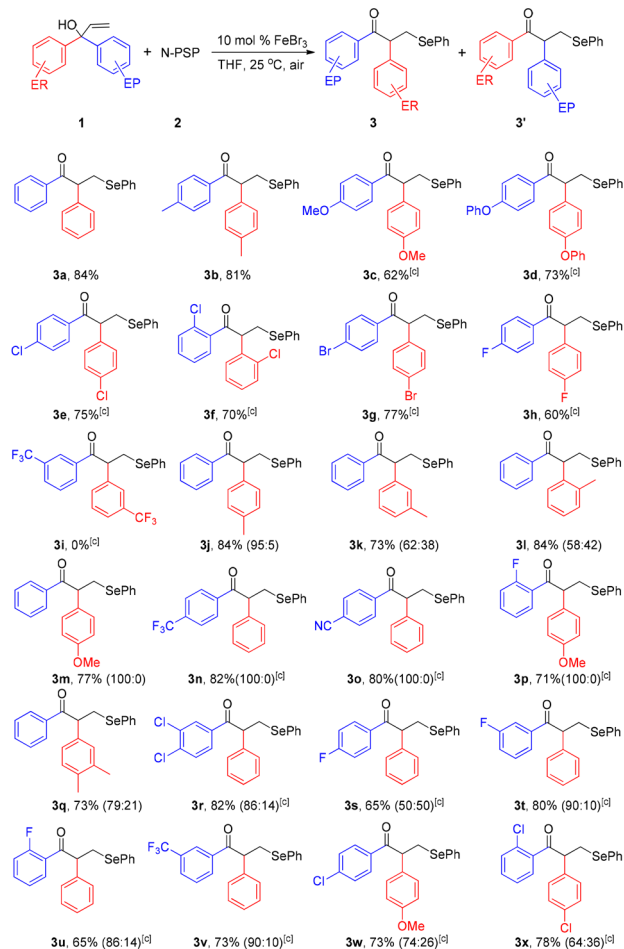
In order to explore the diversity of difunctionalization of alkenes, such a radical 1,2-aryl migrating preference should be circumvented by altering the reaction pathway. Organoselenium compounds have demonstrated potential applications in organic synthesis.⁸ However, selenylation-initiated difunctionalization of

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alkenes has not yet been documented although diverse alkene difunctionalization methods have recently been established. During the ongoing investigation of organoselenium chemistry in organic synthesis,⁹ we reasonably envisioned that *N*-(phenylseleno)phthalimide (N-PSP)¹⁰ might be used to initiate the difunctionalization reactions of allylic alcohols by its ready generation of phenylselenium cation (PhSe⁺) under mild conditions. The strategy includes addition of the PhSe⁺ cation to an olefinic C=C bond to yield an episelenonium ion intermediate which thus renders a cationic group migration.¹¹ Due to the advantages of a simple iron salt as the catalyst or promotor over other transition-metal compounds,¹² we utilized an iron salt to promote the generation of the PhSe⁺ cation from N-PSP to initiate the designed difunctionalization reactions of alkenes. Herein, we disclose an iron-promoted tandem phenylselenylation/1,2-aryl migration of allylic alcohols under mild conditions (Scheme 1b).

Initially, the reaction of α,α -diphenyl allylic alcohol (**1a**) and N-PSP (**2**) was conducted to optimize the reaction conditions for the formation of α -phenyl- β -phenylselenenyl ketone (**3a**). The reaction conditions were optimized to a molar ratio of **1a**:**2** = 1:1, 10 mol % FeBr₃ as the catalyst, THF as the solvent, 25 °C, and 0.5 h in air (see the Supporting Information (SI) for details). Under the optimal conditions, the scope of allylic alcohols **1** was explored (Scheme 2). Symmetrical α,α -diaryl allylic alcohols (**1a**–**1h**) were applied to undergo the reactions with **2** on a 0.5 mmol scale, affording the target products of type **3**. Thus, α -phenyl- β -phenylselenenyl ketone **3a** was obtained in 84% yield, and α,α -di(4-methylphenyl) allylic alcohol (**1b**) reacted to form **3b** in a comparative yield (81%). An obvious negative electronic effect from 4-methoxy on the aryl moiety led to inefficient formation of **3c** (62%). Unexpectedly, a 4-phenoxy substituent did not exhibit a detrimental impact on the reaction efficiency as 4-methoxy did, and the desired reaction gave **3d** in 73% yield by using 20 mol % FeBr₃. α,α -Di(haloaryl) allylic alcohols exhibited good reactivity with **2**, affording **3e**–**3g** in 70–77% yields, and only a 4-fluorophenyl-bearing substrate reacted less efficiently to form **3h** (60%). It should be noted that a 4-CF₃ substituent on the aryl moiety deprived the reactivity of the allylic alcohol. In the cases of using unsymmetrical α,α -diaryl allylic alcohols, two kinds of products, that is, ketones **3** and **3'**, could be obtained. Formation of compounds **3** is attributed to the regioselective 1,2-migration of the α -aryl group bearing a relatively electron-rich substituent, while 1,2-migration of the α -aryl group bearing a less electron-rich or relatively electron-poor (deficient) substituent resulted in products of type **3'**. Radical-initiated difunctionalization reactions of α,α -diaryl allylic alcohols formed compounds of type **3'** as the major products.^{3–6} However, compounds **3** were the only or dominant products in our cases. α -Phenyl- α -tolyl allylic alcohols efficiently reacted with **2**, giving the target products **3j**–**3l** in 73–84% yields with preferential 1,2-migration of the tolyl groups. The steric effect from the methyl substituent in the tolyl moiety remarkably affected the regioisomer selectivity of the target products. For the allylic alcohol substrates bearing two α -aryls with significantly different or opposite electronic properties, their reactions with **2** exclusively afforded the regioselective products of type **3**. Thus, **3m** (77%), **3n** (82%), **3o** (80%), and **3p** (71%) were exclusively produced. Such a 1,2-aryl migration preference is contrary to the well-known radical 1,2-aryl migration in the difunctionalization of α,α -diaryl allylic alcohols (Scheme 1a).^{3–6} Following such a 1,2-aryl migration preference, product **3q** (79/21) was obtained in 73% yield, demonstrating the steric effect on the regioisomer selectivity. Compound **3r** (86/14) was formed in

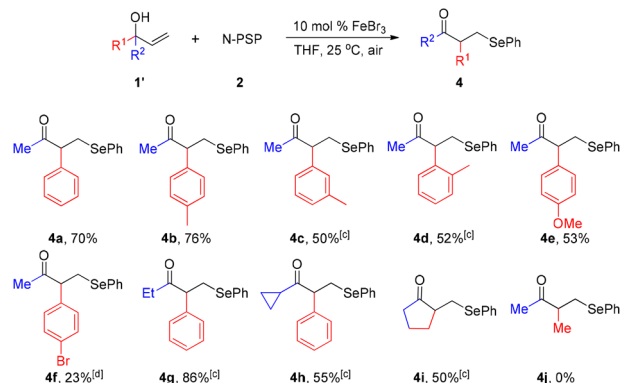
Scheme 2. Scope of α,α -Diaryl Allylic Alcohols (**1**)^{a,b}



^aConditions: **1** (0.5 mmol), **2** (0.5 mmol), FeBr₃ (0.05 mmol), THF (5 mL), 25 °C, 0.5 h. ^bIsolated yields refer to **3** and its isomer. Only the major products are shown with the ratio of **3** to its isomer **3'** given in parentheses through the ¹H NMR determination of the crude product. ^cUsing 20 mol % FeBr₃, 2 h.

82% yield, and the two chloro substituents featured the electron-withdrawing property. Unexpectedly, α -phenyl- α -(4-fluorophenyl) allylic alcohol reacted with **2** to produce **3s** (65%) as a 1:1 mixture of the regioisomers of types **3** and **3'**, while 3- and 2-F substituents differentiated the product selectivities for **3t** (90/10) and **3u** (86/14). α,α -Di(4-CF₃-phenyl) allylic alcohol did not react with **2** under the stated conditions. The preference of aryl migration depends on the electron-donating capability of the chloro and methoxy substituents, and the order 4-OMe > 4-Cl > 2-Cl was unambiguously observed in the formation of **3w** (73%, 74/26) and **3x** (78%, 64/36).

Next, the reactions of α -alkyl- α -aryl allylic alcohols (**1'**) with **2** were investigated to further extend the substrate scope (Scheme 3). Under the standard conditions, α -methyl- α -phenyl allylic alcohol (**1a'**) reacted with **2** to form α -phenyl- β -phenylselenenyl alkyl ketone **4a** in 70% yield with regioselective 1,2-migration of the phenyl group. This migration phenomenon was similar to those radical 1,2-aryl migrations as previously reported.^{3a,4d} The 4-tolyl analog reacted with **2** more efficiently to yield **4b** (76%). However, both α -methyl- α -(3-tolyl) and α -methyl- α -(2-tolyl) allylic alcohols exhibited lower reactivity and required 20 mol % FeBr₃ to form **4c** (50%) and **4d** (52%), respectively. α -Methyl- α -(4-methoxyphenyl) allylic alcohol also reacted well to produce **4e**

Scheme 3. Scope of α -Aryl- α -alkyl Allylic Alcohols (**1'**)^{a,b}

^aConditions: **1'** (0.5 mmol), **2** (0.5 mmol), FeBr_3 (0.05 mmol), THF (5 mL), 25 °C, air, 0.5 h. ^bYields refer to the isolated products. ^cUsing 20 mol % FeBr_3 , 0.5 h. ^dUsing 20 mol % FeBr_3 , 2 h.

(53%). However, α -methyl- α -(4-bromophenyl) allylic alcohol exhibited a poor reactivity to form **4f** in 23% yield. Unexpectedly, α -ethyl- α -phenyl allylic alcohol could efficiently react with **2** to afford **4g** (86%). α -Cyclopropyl- α -phenyl allylic alcohol reacted to produce **4h** in a moderate yield (55%), while two types of products including the 1,2-cyclopropyl migration product were obtained in its radical-initiated difunctionalization.^{4c} The α -methyl allylic alcohol bearing electron-deficient 4- CF_3 -phenyl did not undergo the reaction. 1-Vinylcyclobutanol also reacted with **2** to yield the ring-expansion product **4i** (50%), but transformation of 1-vinylcyclopentanol to cyclohexanone could not be realized, and α,α -dimethyl allylic alcohol could not react to form **4j** either.

The applicability of the resultant α -aryl- β -phenylselenenyl ketones **3** and **4** was investigated. Treatment of **3** or **4** with 2,4-dinitrophenylhydrazine (**5**) in the presence of boron trifluoride etherate¹³ in refluxing methanol resulted in hydrazones **6** (42–88%) (Table 1). Compounds **3** and **4** were liquid at ambient temperature, and it is impossible to determine their solid-state molecular structures. To our delight, the hydrazine derivatives of **3** and **4** were solid at ambient temperature and the single crystals of hydrazones **6e** and **6g** were successfully obtained for the X-ray structural determinations (see the SI for details). It is unambiguously demonstrated that in the reactions of α,α -diaryl allylic alcohols **1** with **2** to form compounds **3m** and **3p** (Scheme 2), the relatively electron-rich aryl groups (4-MeO-phenyl vs phenyl and 2-F-phenyl) preferentially underwent the 1,2-migration.

Removal of phenylselenenyl moiety from compounds **6** was attempted by means of *m*-chloroperoxybenzoic acid (*m*-CPBA), H_2O_2 , and tri-*n*-butyltin hydride ($n\text{Bu}_3\text{SnH}$).⁹ Unfortunately, no dephenylselenenylation reaction occurred. To our delight, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ could efficiently catalyze the dehydrophenylselenenylation of compounds **6** in DMSO at 120 °C, affording 2-pyrazoline derivatives **7a–7g** (71–90%) and **7i** (85%), respectively (Table 1, entries 1–7 and 9). In the case of using **3r** the target product **7h** was obtained in a relatively low yield (59%) (Table 1, entry 8). Starting from the mixture of regioisomers **3s** and **3s'** (50/50), a mixture product of **7i** and **7i'** with the unchanged molar ratio 50:50 was obtained (Table 1, entry 9). In a similar fashion, the mixture product of **7j** and **7j'** was also obtained (Table 1, entry 10). It is noteworthy that the corresponding hydrazones **6k–6n** of ketones, **4a**, **4g**, **4h**, and **4i** were also prepared (73–86%), but they could not undergo the catalytic dehydrophenylselenenylation reactions (see the SI).

Table 1. Hydrazone and Dehydrophenylselenenylation^a

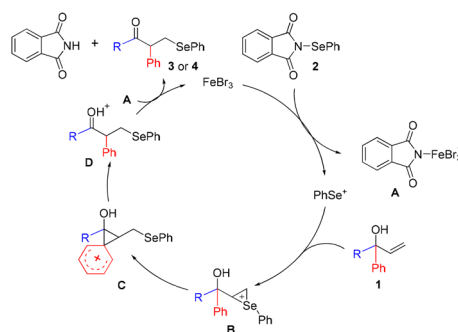
entry		6	7	entry	6	7
1		6a, 62%		6		
2		6b, 15 h, 86%		7		
3		6c, 24 h, 88%		8		
4		6d, 23 h, 42%		9		
5		6e, 6 h, 57%		10		

^aConditions A: **3** or **4** (0.2 mmol), **5** (0.2 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (0.4 mmol), MeOH (2 mL), 65 °C; Conditions B: **6** (0.1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.01 mmol), DMSO (1 mL), 120 °C, air, 0.5 h. Yields refer to the isolated products. $\text{Ar}' = 2,4\text{-(O}_2\text{N)}_2\text{C}_6\text{H}_3$.

Pyrazolines are important five-membered azaheterocycles which can act as useful synthetic building blocks,¹⁴ and the pyrazoline motif exists in many biologically active compounds.¹⁵ Although diverse methods have been reported for their synthesis,^{16,17} the present synthetic method provides an alternative route to functionalized pyrazoline derivatives.

To explore the reaction mechanism, the reaction of **1a** and **2** was conducted in the presence of 2 equiv of a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-tert-butyl-4-methylphenol (BHT), and the target product **3a** was obtained in 78–82% yields. These results excluded a radical

Scheme 4. Proposed Mechanism for Tandem Phenylselenenylation/1,2-Aryl Migration of Allylic Alcohols



pathway. Thus, a plausible reaction mechanism is proposed in Scheme 4.^{8c} Interaction of Lewis acid FeBr₃ with 2 initially generates the phenylselenium cation (PhSe⁺) as well as anion A. Subsequent addition of PhSe⁺ cation to the olefinic C=C bond in allylic alcohol 1 forms episelenium ion B^{8a} which undergoes intramolecular ring-opening by the nucleophilic attack of the α -aryl group to yield dearomatic cation C. 1,2-Aryl migration is thus established to yield protonated ketone intermediate D. Deprotonation by anion A affords the target product 3 or 4 with regeneration of FeBr₃.

In conclusion, iron-promoted phenylselenylation with concomitant 1,2-aryl migration of allylic alcohols was efficiently realized under mild conditions. In contrast to the radical 1,2-aryl migration in the difunctionalization of α,α -diaryl allylic alcohols, the PhSe⁺-initiated process has demonstrated an opposite preference for 1,2-aryl migration. The present method provides a new difunctionalization strategy of alkenes and offers an alternative route to functionalized pyrazoline derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02751.

Experimental materials and procedures, NMR of compounds, and X-ray crystallographic analysis for compounds 6e and 6g (PDF)

Crystallographic data for compounds 6e and 6g (CIF)

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Notes

The authors declare no competing financial interest.

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