

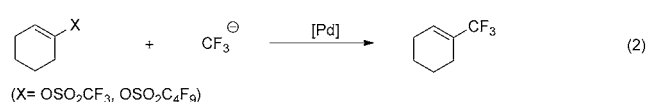
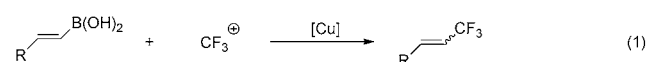
Copper-Catalyzed Di- and Trifluoromethylation of α,β -Unsaturated Carboxylic Acids: A Protocol for Vinylic Fluoroalkylations**

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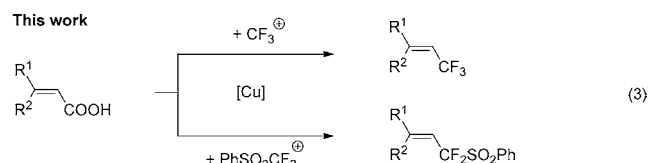
The incorporation of fluorinated moieties into organic molecules can often result in profound and useful changes in their physical, chemical, and biological properties.^[1] In medicinal chemistry, for example, the selective incorporation of a trifluoromethyl (CF_3) or difluoromethyl (CF_2H) group into drug candidates often dramatically alters their stability, lipophilicity, bioavailability, and biopotency.^[2] Hence, it has been of great synthetic interest to develop efficient methods for the incorporation of the CF_3 or CF_2H group into organic molecules. However, although a variety of processes for the construction of $\text{C}_{\text{sp}^3}\text{--CF}_3$ (or $\text{C}_{\text{sp}^3}\text{--CF}_2\text{H}$) bonds have been developed,^[3] there are fewer processes for the construction of $\text{C}_{\text{sp}^2}\text{--CF}_3$ (or $\text{C}_{\text{sp}^2}\text{--CF}_2\text{H}$) bonds. Currently, the reaction between an aryl (or vinyl) halide and a stoichiometric amount of a CF_3Cu reagent represents the most widely used method for the construction of $\text{C}_{\text{sp}^2}\text{--CF}_3$ bonds,^[4] yet a similar process for $\text{C}_{\text{sp}^2}\text{--CF}_2\text{H}$ bond formation has been challenging owing to the thermal instability of $(\text{CF}_2\text{H})\text{Cu}$ species.^[5] In addition, the past three years has witnessed rapid advances in copper- and palladium-catalyzed trifluoromethylation reactions for the construction of $\text{C}_{\text{aryl}}\text{--CF}_3$ bonds.^[4,6,7] However, transition-metal-catalyzed trifluoromethylations for the direct construction of $\text{C}_{\text{vinyl}}\text{--CF}_3$ bonds have not been well developed. Recently, the groups of Liu and Shen reported copper(I)-catalyzed reaction of vinylboronic acids with electrophilic trifluoromethylation reagents [Eq. (1)]^[6f,g] and Cho and Buchwald reported a palladium(0)-catalyzed trifluoromethylation of cyclohexenyl sulfonates with nucleophilic trifluoromethylation reagents [Eq. (2)].^[8] However, the process by Liu and Shen produces a mixture of trifluoromethylated alkene stereoisomers,^[6f,g] and the process by Cho and Buchwald was shown to be effective only with six-membered cyclohexenyl sulfonates.^[8] Furthermore, to the best of our knowledge, the metal-catalyzed construction of $\text{C}_{\text{vinyl}}\text{--CF}_2\text{R}$ ($\text{R} \neq \text{F}$) bonds has never been reported. Therefore, an efficient and general protocol for the catalytic di- and trifluoromethylations of vinylic carbon atoms is highly desired.

Carboxylic acids are ubiquitous compounds in organic chemistry, which are commercially available in a large variety.^[9] Recently, carboxylic acids have been frequently used as attractive reactants for metal-catalyzed decarboxylative C–C cross-coupling reactions.^[9–11] However, to the best of our knowledge, selective fluoroalkylation (such as di- and trifluoromethylation) of nonfluorinated carboxylic acids with fluoroalkylating agents through a decarboxylative fluoroalkylation protocol has never been reported [Eq. (3)]. Herein, we disclose our success in developing a new powerful protocol for vinylic di- and trifluoromethylation through the copper-catalyzed decarboxylative fluoroalkylation of α,β -unsaturated carboxylic acids with a Togni-type electrophilic fluoroalkylating agent^[12,13] [Eq. (3)].

Previous work



This work



At the onset of our investigation, we chose the reaction between the $\text{I}^{\text{III}}\text{--CF}_2\text{SO}_2\text{Ph}$ reagent (**1a**) and 3,3-diphenylacrylic acid (**2a**) as a model reaction to survey the reaction conditions, thus taking advantage of the ready availability of **1a** in our group.^[13] As shown in Table 1, when $\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ was used as the catalyst, it was found that both solvent and temperature were crucial for the reaction. It is particularly interesting that the addition of water as a cosolvent and tetramethylethylenediamine (TMEDA) as an additive can significantly increase the yield of the product, and the ratio of the mixed solvents also influences the yield (entries 1–4 and 11–15). Lowering the amount of the catalyst and the reaction temperature decreases the yield (entries 9, 10, 12, and 16). Finally, the optimal yield of product **3a** (73 %) was obtained when **1a** and **2a** (molar ratio 1:3.0) were stirred in $\text{H}_2\text{O}/\text{DCE}$ (4:3) in the presence of $\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ (20 mol %) and TMEDA (25 mol %) at 80 °C for 12 hours (entry 12).

By using the optimized reaction conditions (Table 1, entry 12), we next examined the substrate scope of the present copper-catalyzed decarboxylative fluoroalkylation

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Table 1: Survey of reaction conditions.

$\text{PhSO}_2\text{F}_2\text{C}-\text{I}-\text{O} + \text{Ph}-\text{CH}=\text{CH}-\text{COOH} \xrightarrow[\text{solvent, } T, 12 \text{ h}]{\text{CuF}_2 \cdot 2\text{H}_2\text{O (cat.)}} \text{Ph}-\text{CH}=\text{CH}-\text{CF}_2\text{SO}_2\text{Ph}$						
1a (1.0 equiv)		2a	3a			
Entry	Equiv 2a	Solvent ^[a]	Equiv CuF ₂ ·2H ₂ O	Equiv TMEDA	T [°C]	Yield [%] ^[b]
1	2.0	1,4-dioxane	0.20	—	80	10
2	2.0	DME	0.20	—	80	15
3	2.0	H ₂ O/DME (1:4)	0.20	—	80	20
4	2.0	H ₂ O/1,4-dioxane (1:4)	0.20	—	80	25
5	2.0	H ₂ O/CH ₃ CN (1:4)	0.20	—	80	31
6	2.0	H ₂ O/DMF (1:4)	0.20	—	80	trace
7	2.0	H ₂ O/CCl ₄ (2:3)	0.20	—	80	35
8	2.0	H ₂ O/DCE (2:3)	0.20	—	80	43
9	2.0	H ₂ O/DCE (2:3)	0.20	0.25	80	61
10	2.0	H ₂ O/DCE (2:3)	0.05	0.25	80	52
11	3.0	H ₂ O/DCE (2:3)	0.20	0.25	80	65
12	3.0	H ₂ O/DCE (4:3)	0.20	0.25	80	73
13	3.0	H ₂ O/DCE (4:1)	0.20	0.25	80	61
14	3.0	H ₂ O/DCE (1:4)	0.20	0.25	80	57
15	3.0	DCE	0.20	0.25	80	52
16	3.0	H ₂ O/DCE (4:3)	0.20	0.25	50	51
17	3.0	H ₂ O/DCE (4:3)	0.30	0.25	80	60
18	3.0	H ₂ O/DCE (4:3)	0.20	0.40	80	62

[a] The data in the parentheses refer to the volume ratio. [b] Determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard. DCE = 1,2-dichloromethane, DME = 1,2-dimethoxyethane, DMF = *N,N*-dimethylformamide, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

reaction. The results are summarized in Table 2. The reaction proved to be general and amenable to a range of structurally diverse substrates (**2a–t**, all with an *E* configuration), and the desired products **3a–t** were produced in satisfactory yields. We found that both electron-rich and electron-deficient aryl-substituted acids reacted with **1a** to give products such as **3b–j** in excellent yields. Furthermore, heteroaryl-substituted α,β -unsaturated carboxylic acids are also viable substrates in the current reaction, thus giving the corresponding heteroaryl-substituted alkenes (**3k, 3l, 3m**, and **3r**). It is worthwhile mentioning that the alkyl-substituted α,β -unsaturated carboxylic acid **2t** was also found to react smoothly with **1a** to give the corresponding product **3t** in good yield. Notably, the reactions were found to be highly stereoselective, with only the *E* isomer of the product being observed in each case (Table 2). Since the (phenylsulfonyl)difluoromethyl group is a versatile functionality that can be readily transformed into the difluoromethyl (CF₂H) group,^[14] the present synthetic method opens up a new avenue for the construction of C_{vinyl}–CF₂H bonds.

Encouraged by the aforementioned (phenylsulfonyl)-difluoromethylation reactions, we extended the reaction to trifluoromethylation by using Togni's reagent **1b**.^[12] After a quick scanning of the reaction conditions (see Table S-1 in the Supporting Information), we found that under similar reaction conditions, the reactivity of reagent **1b** was somewhat different from that of **1a**. Consequently, we modified the reactant ratio to **4/1b**=4:1. The data are summarized in

Table 2: (Phenylsulfonyl)difluoromethylation of α,β -unsaturated carboxylic acids **2** with reagent **1a**.^[a,b]

$\text{PhSO}_2\text{F}_2\text{C}-\text{I}-\text{O} + \text{R}^1-\text{CH}=\text{CH}-\text{COOH} \xrightarrow[\text{H}_2\text{O/DCE, } 80^\circ\text{C, } 12 \text{ h}]{\text{CuF}_2 \cdot 2\text{H}_2\text{O (20 mol\%)}, \text{TMEDA (25 mol\%)}} \text{R}^1-\text{CH}=\text{CH}-\text{CF}_2\text{SO}_2\text{Ph}$				
1a	2			3
3a , 70%	3b , 88%	3c , 86%	3d , 90%	
3e , 87%	3f , 91%	3g , 86%	3h , 87%	
3i , 86%	3j , 82%	3k , 76%	3l , 60%	
3m , 60%	3n , 90%	3o , 84%	3p , 84%	
3q , 73%	3r , 70%	3s , 65%	3t , 63%	

[a] A mixture of **1a** (0.6 mmol), **2** (1.8 mmol), CuF₂·2H₂O (0.12 mmol, ca. 20 mol %), TMEDA (0.15 mmol, ca. 25 mol %), DCE (3 mL), H₂O (4 mL) was stirred at 80°C for 12 h. [b] Yield of isolated product.

Table 3. It was found that, the trifluoromethylation of α,β -unsaturated carboxylic acids **4** (all with an *E* configuration) bearing electron-rich aryl substituents proceeded smoothly to afford the corresponding CF₃-containing products **5** in moderate to good yields. The reactions with electron-deficient substrates, however, gave lower yields of product (Table 3). Notably, the trifluoromethylation reaction was also found to be stereoselective, with the CF₃-functionalized alkenes **5a–k** being formed with an *E/Z* ratio ranging from 92:8 to greater than 99:1 (Table 3). The major *E* isomers of the products **5a–k** could be purified by silica gel chromatography.

To gain some mechanistic insights into the current decarboxylative fluoroalkylation reaction, two sets of comparative experiments were designed (Scheme 1). Firstly, while the reaction between **1a** and carboxylic acid **2s** gave the desired product **3s** in 65% yield, a similar reaction between **1a** and (*E*)-trimethyl(styryl)silane (**6**) did not furnish the

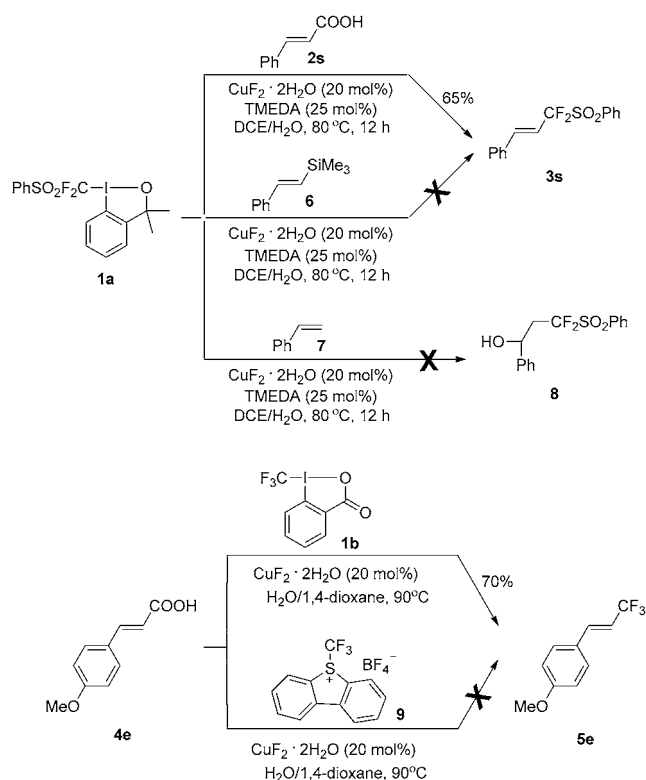
Table 3: Trifluoromethylation of α,β -unsaturated carboxylic acids **4** with reagent **1b**.^[a,b,c]

5a, 42% (E only)	5b, 74% (E/Z = 95/5)
5c, 66% (E only)	5d, 60% (E/Z = 95/5)
5e, 70% (E only)	5f, 60% (E/Z = 92/8)
5g, 62% (E/Z = 98/2)	5h, 52% (E only)
5i, 44% (E only)	5j, 60% (E/Z = 94/6)
5k, 52% (E only)	

[a] A mixture of **1b** (0.8 mmol), **4** (3.2 mmol), $\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ (0.16 mmol, ca. 20 mol %), 1,4-dioxane (4 mL), H_2O (1 mL) was stirred at 80 °C for 12 h. [b] Yield of isolated *E* isomer of the product. [c] *E/Z* ratio was determined by ^{19}F NMR spectroscopy of the crude product mixture.

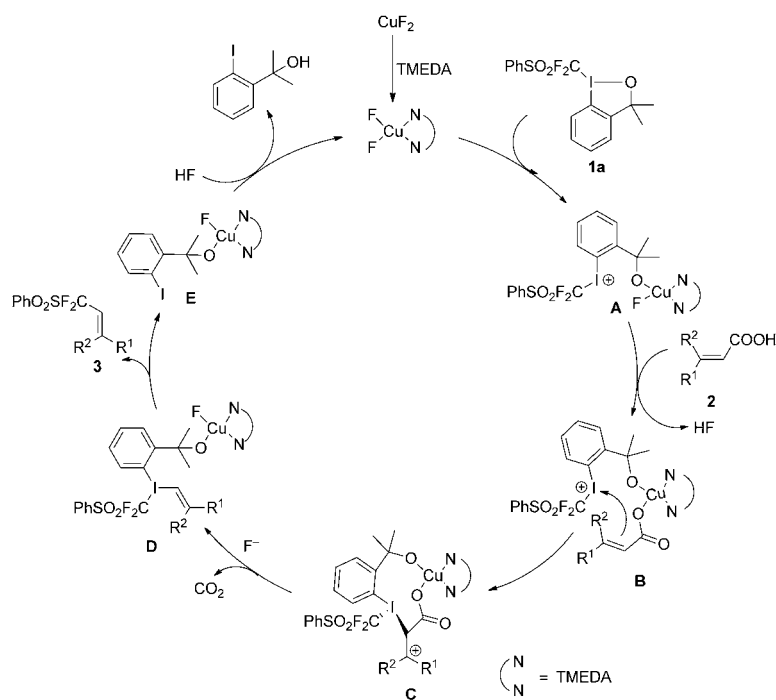
product **3s**. In contrast, the reaction between **1a** and styrene did not deliver the fluoroalkylated product **8**. These results indicate that the presence of a carboxylic acid group in substrates plays an important role for the success of the efficient $\text{C}-\text{R}^{\text{F}}$ (R^{F} = fluorinated alkyl groups) formation reaction. Secondly, as mentioned shown Table 3, carboxylic acid **4e** readily reacted with Togni's reagent **1b** to give the corresponding CF_3 -containing product **5e** in 70 % yield. However, when we replaced the Togni's reagent **1b** with another electrophilic trifluoromethylating agent, **9** (Umemoto reagent),^[15] the formation of the desired product **5e** was not observed, which suggests that the use of Togni-type reagents **1a,b** is important to the success of current decarboxylative fluoroalkylation reaction.

Based on the experimental results, we propose a plausible reaction mechanism for the current copper-catalyzed decarboxylative fluoroalkylations (Scheme 2). The hypervalent iodine reagent **1a** should undergo a copper-catalyzed bond cleavage to generate the highly electrophilic iodonium salt **A**, which then coordinates to the carboxylic acid functionality to generate the intermediate **B**. **B** then undergoes an intramolecular reaction between the alkene functionality



Scheme 1. The importance of both the carboxylic acid functionality and Togni-type reagents for the reaction.

and the iodonium ion to afford the intermediate **C**. The intermediate **C** then undergoes decarboxylation^[16] to give the thermodynamically stable *E*-alkene intermediate **D**, which undergoes reductive elimination to generate the species **E**



Scheme 2. Proposed reaction mechanism.

and the desired product **3** (with an *E* configuration). Species **E** reacts with H^+ to liberate the catalyst.

In summary, we have developed a new strategy for the vinylic C–R^F bond formation, that is, Lewis acid catalyzed di- and trifluoromethylation of α,β -unsaturated carboxylic acids through decarboxylative fluoroalkylation. A wide range of α,β -unsaturated carboxylic acids (including alkyl- and aryl-substituted ones) were subjected to the present reaction conditions and furnished the corresponding di- and trifluoromethylated alkenes in high yields and with excellent *E/Z* selectivity. The Lewis acid ($CuF_2 \cdot 2H_2O$) was found to play an important role in the reaction by both enhancing the electrophilicity of Togni-type reagents and promoting the decarboxylation of α,β -unsaturated carboxylic acids.

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- [1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**; b) *Organofluorine Compounds: Chemistry and Applications* (Ed.: T. Hiyama), Springer, New York, **2000**; c) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**; d) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, *117*, 218; *Angew. Chem. Int. Ed.* **2005**, *44*, 214.
- [2] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; c) J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465.
- [3] a) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119; b) J.-A. Ma, D. Cahard, *J. Fluorine Chem.* **2007**, *128*, 975; c) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757; d) R. P. Singh, J. M. Shreeve, *Tetrahedron* **2000**, *56*, 7613; e) B. R. Langlois, T. Billard, *Synthesis* **2003**, 185; f) T. Umemoto, *Chem. Rev.* **1996**, *96*, 1757; g) Ref [2c].
- [4] O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475.
- [5] a) K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.* **2011**, *13*, 5560; b) Ref [2c].
- [6] a) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909; b) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679; c) X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648; d) L. Chu, F.-L. Qing, *Org. Lett.* **2010**, *12*, 5060; e) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Angew. Chem.* **2011**, *123*, 1936; *Angew. Chem. Int. Ed.* **2011**, *50*, 1896; f) J. Xu, D.-F. Luo, B. Xiao, Z.-J. Liu, T.-J. Gong, Y. Fu, L. Liu, *Chem. Commun.* **2011**, *47*, 4300; g) T. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342; h) A. T. Parsons, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 9286; *Angew. Chem. Int. Ed.* **2011**, *50*, 9120; i) J. Xu, Y. Fu, D.-F. Luo, Y.-Y. Jiang, B. Xiao, Z.-J. Liu, T.-J. Gong, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 15300; j) X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 16410; k) H. Kawai, T. Furukawa, Y. Nomura, E. Tokunaga, N. Shibata, *Org. Lett.* **2011**, *13*, 3596.
- [7] T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470.
- [8] E. J. Cho, S. L. Buchwald, *Org. Lett.* **2011**, *13*, 6552.
- [9] L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem.* **2008**, *120*, 3144; *Angew. Chem. Int. Ed.* **2008**, *47*, 3100.
- [10] J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846.
- [11] O. Baudoin, *Angew. Chem.* **2007**, *119*, 1395; *Angew. Chem. Int. Ed.* **2007**, *46*, 1373.
- [12] a) R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann, A. Togni, *Angew. Chem.* **2009**, *121*, 4396; *Angew. Chem. Int. Ed.* **2009**, *48*, 4332; b) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986; c) K. Niedermann, N. Frueh, E. Vinogradova, M. S. Wiehn, A. Moreno, A. Togni, *Angew. Chem.* **2011**, *123*, 1091; *Angew. Chem. Int. Ed.* **2011**, *50*, 1059; d) R. Koller, Q. Huchet, P. Battaglia, J. M. Welch, A. Togni, *Chem. Commun.* **2009**, 5993; e) S. Fantasia, J. M. Welch, A. Togni, *J. Org. Chem.* **2010**, *75*, 1779.
- [13] a) W. Zhang, J. Zhu, J. Hu, *Tetrahedron Lett.* **2008**, *49*, 5006; b) J. Hu, *J. Fluorine Chem.* **2009**, *130*, 1130.
- [14] a) Y. Li, H. Li, J. Hu, *Tetrahedron* **2009**, *65*, 478; b) Ref. [13b]; c) G. K. S. Prakash, J. Hu, *Acc. Chem. Res.* **2007**, *40*, 921.
- [15] a) Ref. [3f]; b) N. Shibata, A. Matsnev, D. Cahard, *Beilstein J. Org. Chem.* **2010**, *6*, 65.
- [16] Copper salts have been previously used to enhance the decarboxylation of carboxylic acids. See: Q.-Y. Chen, S.-W. Wu, *J. Fluorine Chem.* **1989**, *44*, 433.