Synthetic Methods

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Rapid Access to β-Trifluoromethyl-Substituted Ketones: Harnessing Inductive Effects in Wacker-Type Oxidations of Internal Alkenes**

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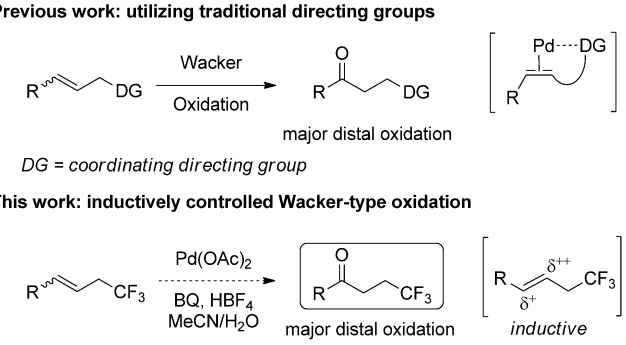
Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *We present a practical trifluoromethyl-directed Wacker-type oxidation of internal alkenes that enables rapid access to β-trifluoromethyl-substituted ketones. Allylic trifluoromethyl-substituted alkenes bearing a wide range of functional groups can be oxidized in high yield and regioselectivity. The distance dependence of the regioselectivity was established by systematic variation of the number of methylene units between the double bond and the trifluoromethyl group. The regioselectivity enforced by traditional directing groups could even be reversed by introduction of a competing trifluoromethyl group. Besides being a new powerful synthetic method to prepare fluorinated molecules, this work directly probes the role of inductive effects on nucleopalladation events.*

Organofluorine compounds are important for the pharmaceutical, agrochemical, and materials industries.[1–4] The incorporation of fluorine into organic molecules can significantly alter their chemical, physical, and biological properties, such as molecular conformation, basicity, lipophilicity, and metabolic stability. An estimated 25% of the marketed drugs contain fluorine.[2b–d] However, the synthesis of fluorine-containing compounds remains a challenge for target-oriented synthesis because of the low abundance of organofluorine compounds from traditional chemical feedstocks.[2-b,5a,b] Hence, significant efforts have been directed towards the development of efficient methods for the synthesis of this important class of compounds.[5,6] Unfortunately, β-trifluoromethyl-substituted ketones remain challenging to prepare, despite their potential as versatile fluorinated building blocks.[7]

In principle, a Wacker oxidation[8] of readily available[6a–d] alkenes bearing an allylic trifluoromethyl group could provide practical and rapid access to β-trifluoromethyl-substituted ketones. Traditionally, directing groups capable of coordinating to the palladium center have been exploited to control the regioselectivity of the Wacker reaction. In contrast, trifluoromethyl groups are relatively noncoordinating and their influence on regioselectivity remains to be established. Recent progress has enabled the Wacker-type oxidation of internal alkenes,[9] and as we explored the regioselectivity in one such system, we discovered that more electron deficient directing groups provide higher regioselectivity.[9g] Thus, we hypothesized that strongly electron-withdrawing substituents could enable the highly regioselective oxidation of internal alkenes at the distal position without having to rely upon chelation assistance (Scheme 1).[9b–g,10a]



Scheme 1. Regiocontrol in Wacker oxidations of internal alkenes. BQ = *p*-benzoquinone.

In contrast to Tsuji–Wacker conditions, which proved unreactive towards these electron-deficient internal alkenes,[10] our recently reported procedure for the Wacker-type oxidation of internal alkenes resulted in good conversions and excellent regioselectivities.[9c,g] The optimum reaction conditions were found to be 7.5 mol% $Pd(OAc)_2$ and a stoichiometric amount of *p*-benzoquinone in $MeCN/H_2O$ (7:1) for 24 h at 40 °C.[11] Under these conditions, a variety of alkenes bearing allylic trifluoromethyl groups could be oxidized in 70–91% yield. As predicted by the inductive hypothesis, each example exhibited excellent (≥20:1) regioselectivity for the distal oxidation product (Table 1).[12] The newly developed procedure tolerates a variety of synthetically useful, orthogonal alcohol protecting groups (entries 1–4) and amine precursors (entries 5 and 6). Even alkenes containing unprotected alcohols (entry 7) could be oxidized chemoselectively. The excellent functional-group tolerance of this reaction was further demonstrated by its compatibility with nitriles (entry 8), tosylates (entry 9), and primary alkyl halides (entry 10). In all cases, selectivities of ≥20:1 (distal oxidation

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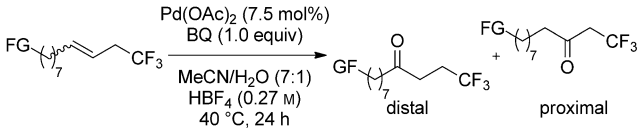
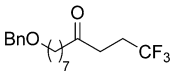
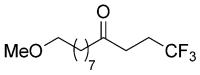
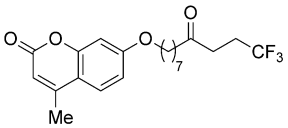
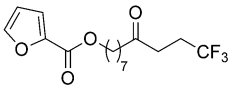
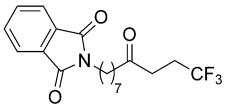
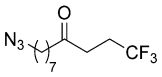
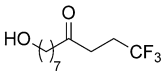
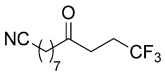
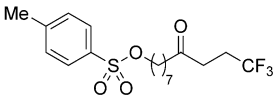
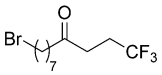
Table 1: Substrate scope of the CF_3-directed Wacker oxidation of internal alkenes.[a,b]

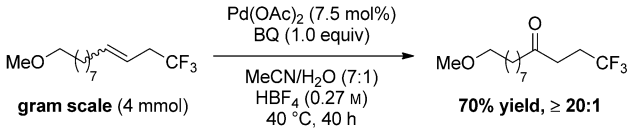


Entry	Product	Yield[c]	Sel.[d]
1[e]		72	≥20:1
2		91	≥20:1
3		70	≥20:1
4		75	≥20:1
5		85	≥20:1
6		77	≥20:1
7		84	≥20:1
8		75	≥20:1
9		82	≥20:1
10[f]		74	≥20:1

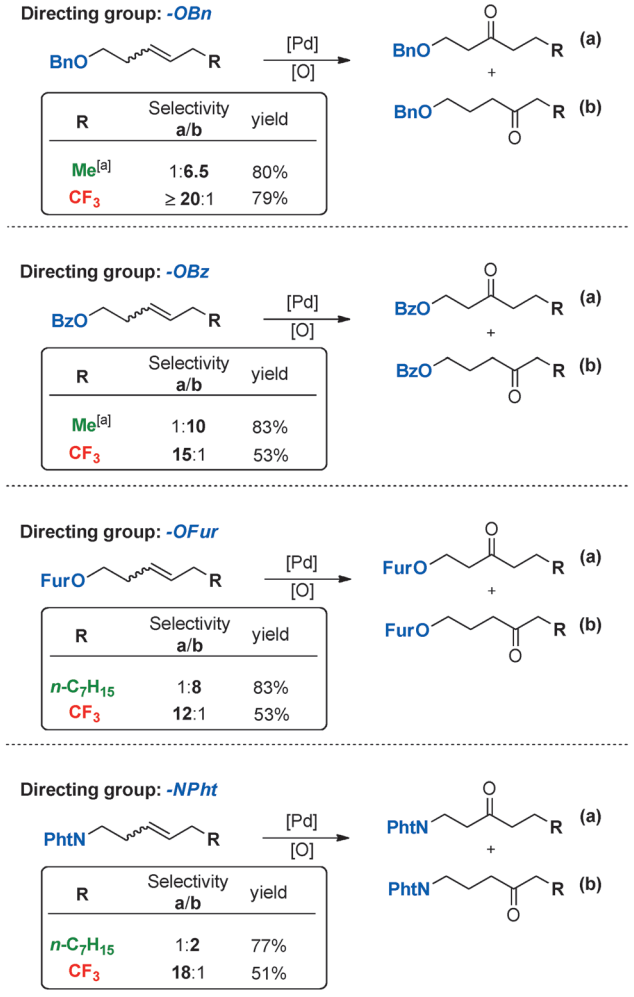
[a] 0.25 mmol alkene. [b] *E*/*Z* ratio between 5:1 and 10:1. [c] Yield of isolated products. [d] Sel. = distal oxidation/proximal oxidation, as determined by ^{19}F and ^{1}H NMR analysis of the crude reaction mixture. [e] 0.5 mmol alkene. [f] 0.21 mmol alkene.

over proximal oxidation) were obtained and further establish the previously unprecedented[13] powerful directing effect of the trifluoromethyl group in Wacker-type oxidations of internal alkenes.

We then probed the efficiency of the procedure on a preparatively useful scale. The reaction of 1,1,1-trifluoro-12-methoxydodec-3-ene (Table 1, entry 2) on a gram scale (4 mmol) proceeded in 70% yield and in ≥20:1 selectivity for the distal oxidation product. This scalability combined with the reliance upon only commercially available (and comparatively inexpensive) reagents bodes well for the immediate application of this reaction in target-oriented synthesis.



Next, we sought to probe the directing power of the trifluoromethyl group relative to classical Wacker directing groups. To this end, a series of intramolecular competition experiments was designed and executed to directly compare the influence of functional groups proximal to the double bond (Scheme 2).[14] To more precisely evaluate the influence of the trifluoromethyl group on the observed selectivities, we additionally probed substrates bearing a nondirecting alkyl group in place of the trifluoromethyl group. In each of the investigated cases, the replacement of an alkyl substituent with a trifluoromethyl group led to an inversion of selectivity, thereby demonstrating that the predominantly inductive trifluoromethyl group can override the regiocontrol provided

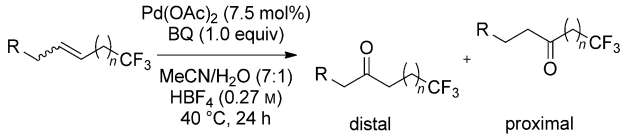


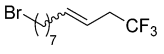
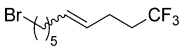
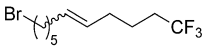
Scheme 2. Intramolecular competition experiments to probe the effect of the trifluoromethyl group: $Pd(OAc)_2$ (7.5 mol%), BQ (1.0 equiv), $MeCN/H_2O$ (7:1), HBF_4 (0.27 M), 40 °C, 24 h. Bn = benzyl; Bz = benzoyl; Fur = 2-furoyl, PhtN = phthalimide. [a] Results reproduced from Ref. [9g].

by traditional coordinating groups. For example, a homoallylic 2-furoyl ester results in selective oxidation to product **b** (**a**/**b** 1:8). However, upon introduction of the trifluoromethyl group, the observed regioselectivity is reversed and the alkene is selectively oxidized to product **a** (**a**/**b** 12:1). Furthermore, the introduction of the trifluoromethyl group is strong enough to override the selectivity determined by the benzoate group, a group known for its powerful directing ability (**a**/**b** 1:10 versus 15:1). These competition experiments thus further illustrate the powerful directing ability of the trifluoromethyl group for the synthesis of valuable fluorinated products. Moreover, these observations offer a platform to predict the regioselectivity of Wacker-type oxidations of internal alkenes bearing potentially competing directing groups, which is critical for the adoption of this oxidation method in target-oriented synthesis.

To probe the distance dependence of the observed directing effects, a series of alkenes bearing trifluoromethyl groups in varied proximity to the alkene were subjected to the catalytic conditions (Table 2). When the distance from the site

Table 2: Distance dependence of the CF_3-directed Wacker oxidation of internal alkenes.[a]

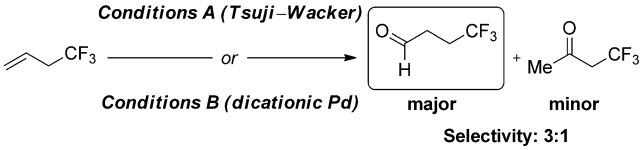


Entry	Substrate	Yield[b]	Sel.[c]
1[d,e]		74	≥20:1
2[f]		86	5.5:1
3[g]		74	1.9:1

[a] 0.1 mmol alkene. [b] Yield of isolated products. [c] Sel. = distal oxidation/proximal oxidation, as determined by ^{19}F and ^{1}H NMR analysis of the crude reaction mixture. [d] 0.21 mmol alkene, see Table 1, entry 10. [e] *E*/*Z* 5:1. [f] *E*/*Z* 1:6. [g] *E*/*Z* 1:16.

of unsaturation was increased, the selectivity for the distal oxidation decreased steadily ($n=1$: ≥20:1; $n=2$: 5.5:1; $n=3$: 1.9:1),[15] in accordance with an inductive model. The synthetically useful selectivity (5.5:1) obtained with a homoallylic trifluoromethyl-substituted substrate (Table 2, entry 2) illustrates the applicability of this strategy to prepare δ-trifluoromethyl-substituted ketones. Even a trifluoromethyl group four bonds away from the alkene (entry 3) exerts an appreciable influence on the regioselectivity (1.9:1).

Having established the powerful directing effect of the trifluoromethyl group on the regioselectivity of Wacker oxidations of internal alkenes, we reasoned that the inductive influence of the trifluoromethyl group could potentially have an impact on the regioselectivity exhibited by terminal alkenes. Under Wacker conditions, terminal alkenes are oxidized with high selectivity to methyl ketones, in accordance with Markovnikov's rule.[8] Based upon our results with internal alkenes, we hypothesized that inductive effects could lead to formal anti-Markovnikov regioselectivity. Thus, 4,4,4-trifluoro-1-butene was subjected to both our standard reaction conditions as well as the classical Tsuji–Wacker conditions (Scheme 3). The alkene was oxidized with full conversion and 3:1 selectivity for the terminal position of the alkene under both procedures.[16] This finding demonstrates the important and general role of inductive effects on nucleopalladation regioselectivity, as, to our knowledge, these results comprise the first examples of achieving a formally anti-Markovnikov Wacker oxidation using inductive effects to reverse the Markovnikov selectivity.[17]



Scheme 3. Influence of inductive effects on the regioselectivity of the Wacker oxidation of terminal alkenes. Quantitative conversion relative to BQ was observed. DMF = *N*,*N*-dimethylformamide. Conditions A (Tsuji–Wacker): $[Pd(PhCN)_2Cl_2]$ (5 mol%), BQ (1.0 equiv), DMF/H_2O (7:1), 40°C, 16 h; conditions B (dicationic Pd): $Pd(OAc)_2$ (7.5 mol%), BQ (1.0 equiv), MeCN/H_2O (7:1), HBF_4 (0.27 M), 40°C, 16 h.

In conclusion, trifluoromethyl groups were shown to be highly efficient directing groups for Wacker-type oxidations, thereby enabling facile access to β-trifluoromethyl-substituted ketones. The broad functional-group tolerance of the oxidation, combined with the readily accessible starting materials, bodes well for the immediate application of the method. Furthermore, we have presented important insight into the selectivity-controlling factors in Wacker-type oxidations of internal alkenes. The inductive influence appears to be a general phenomenon in Wacker-type oxidations, as illustrated by the (3:1) aldehyde selectivity obtained in the Wacker oxidation of 4,4,4-trifluoro-1-butene. Overall, the results described herein provide a foundation for the development of an in-depth understanding of the regioselectivity of nucleopalladation events that will ultimately lead to an improved predictability of Wacker oxidation regioselectivity in target-oriented synthesis.

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[14] For direct comparison, substrates with an allylic trifluoromethyl group and an allylic directing group (-OBn, -OBz, -OFur) were designed and tested. However, these substrates were oxidized in very low conversion.

[15] Compounds containing a vinylic trifluoromethyl group were found to not react under the optimized conditions.

[16] We hypothesize that this selectivity is derived from a combination of the higher stability of the positive charge build up in the transition state at the distal position and the stabilization of negative charge build up at the proximal position effected by the trifluoromethyl group.

[17] For reports that achieved anti-Markovnikov selectivity in Wacker oxidation, see a) J. Muzart, *Tetrahedron* **2007**, *63*, 7505; b) B. W. Michel, A. M. Camelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.* **2009**, *131*, 6076 – 6077; c) B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc.* **2009**, *131*, 9473 – 9474; d) B. W. Michel, J. R. McCombs, A. Winkler, M. S. Sigman, *Angew. Chem.* **2010**, *122*, 7470 – 7473; *Angew. Chem. Int. Ed.* **2010**, *49*, 7312 – 7315; e) M. S. Sigman, E. W. Werner, *Acc. Chem. Res.* **2011**, *44*, 874 – 884; f) G. Dong, P. Teo, Z. K. Wickens, R. H. Grubbs, *Science* **2011**, *333*, 1609 – 1612; g) P. Teo, Z. K. Wickens, G. Dong, R. H. Grubbs, *Org. Lett.* **2012**, *14*, 3237 – 3239; h) J. J. Dong, M. Fañanás-Mastral, P. L. Alsters, W. R. Browne, B. L. Feringa, *Angew. Chem.* **2013**, *125*, 5671 – 5675; *Angew. Chem. Int. Ed.* **2013**, *52*, 5561 – 5565; i) Z. K. Wickens, B. Morandi, R. H. Grubbs, *Angew. Chem.* **2013**, *125*, 11467 – 11470; *Angew. Chem. Int. Ed.* **2013**, *52*, 11257 – 11260; j) Z. K. Wickens, K. Skakuj, B. Morandi, R. H. Grubbs, *J. Am. Chem. Soc.* **2014**, *136*, 890 – 893.

