Alkene Hydrochlorination

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Catalytic Hydrochlorination of Unactivated Olefins with *para*-Toluenesulfonyl Chloride**

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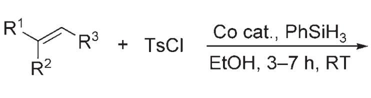
The addition of hydrogen chloride to olefins is one of the first fundamental reactions discussed in introductory organic chemistry. Yet, this simplest of reactions is rather limited in scope, as addition only occurs at useful rates to strained olefins[1] and to alkenes that lead to stabilized carbocationic intermediates.[2] Consequently, the direct hydrochlorination of monosubstituted and functionally rich alkenes remains unprecedented. Yet, the ability to prepare alkyl chlorides directly from a wide range of alkenes would be highly attractive for the synthesis of complex structures. Our ongoing research program in olefin functionalization has led us to examine the hydrochlorination reaction. Herein, we disclose the conversion of unactivated alkenes to alkyl chlorides under mild conditions [Eq. (1)] that is widely tolerant of functionality. Of particular interest is the fact that this unprecedented Co-catalyzed transformation employs *para*-toluenesulfonyl chloride (TsCl) as Cl source.



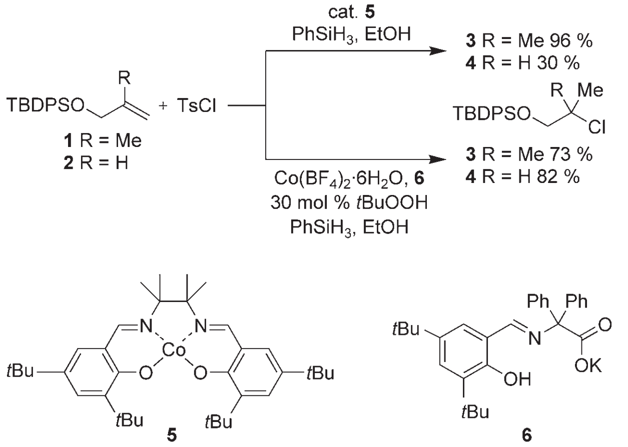
(1)

Lewis acid or surface-mediated reactions of HCl with simple olefins such as cyclohexene and cycloheptene have been reported.[3] However, these and related approaches are intrinsically limited, because they preclude the use of acid-sensitive functional groups common to useful building blocks.[4] A mechanistically distinct palladium-catalyzed process under neutral conditions was recently documented, albeit the addition can only be conducted with styrenes.[5] Moreover, the benzylic chloride adducts were isolable only for electron-poor arenes.

We have reported a series of Co and Mn catalysts that enable the preparation of azides, hydrazine dicarboxylates, and nitriles from olefins.[6–8] The ability to carry out other atom-transfer processes would expand and facilitate the synthesis of novel building blocks accessible from alkenes. The hydrochlorination reaction of olefins is a particularly interesting process to develop, because of the versatility of the organochlorides generated, as such chlorides act as electrophiles in numerous substitution reactions, and they can be transformed into nucleophilic reagents through metalation.

In our initial prospecting experiments, we examined the use of cobalt catalyst **5** and $PhSiH_3$ in combination with silyl ether **1** or **2** (see Scheme 1) as test substrates because these typify alkenes that fail to undergo direct addition by HCl. The more difficult issue involved the identification and selection of a Cl source. We examined a range of potential Cl-transfer reagents, such as NCS, C_2Cl_6, CF_3SO_2Cl, CH_3SO_2Cl, (1*S*)-camphorsulfonyl chloride, methyl 2-chlorosulfonyl benzoate, and $ArSO_2Cl$, where Ar = mesityl, *o*-nitro-, *m*-nitro-, or *p*-methoxyphenyl, 3,4-dimethoxyphenyl, and *p*-tolyl. Methyl 2-chlorosulfonyl benzoate and TsCl showed similar profiles as the only two reagents that were able to promote the formation of the HCl adduct. As TsCl is readily available and widely employed, we decided to investigate the process with this convenient reagent. To the best of our knowledge, the use of TsCl as a Cl-transfer reagent in combination with olefins is unprecedented.

Upon treating **1** with 2 mol% of Co catalyst **5**, $PhSiH_3$, and TsCl in EtOH at ambient temperature (Scheme 1) chloride **3** was isolated in 96% yield after 2.5 h. However, monosubstituted alkene **2** was converted into **4** in merely 30% yield, even at elevated catalyst loadings, namely 5 mol%. With these benchmark results, we decided to optimize the reaction conditions for the more challenging monosubstituted alkene **2**. After screening several catalyst systems we found that the combination of $Co(BF_4)_2{\cdot}6H_2O$ (12 mol%) with ligand **6** (12 mol%) and *t*BuOOH (30 mol%) in the presence of alkene **2** (1 equiv) and phenyl-



Scheme 1. Hydrochlorination of alkenes **1** and **2**.

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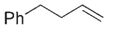
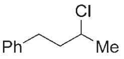
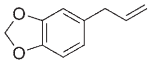
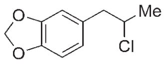
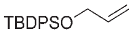
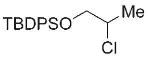
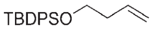
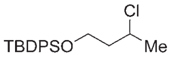
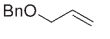
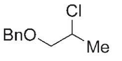
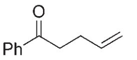
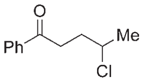
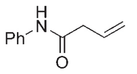
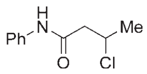
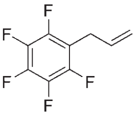
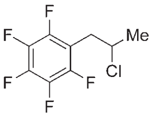
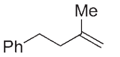
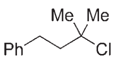
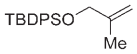
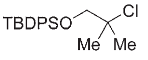
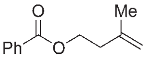
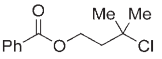
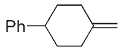
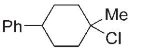
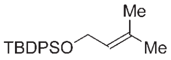
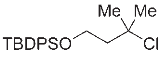
silane (1 equiv) in EtOH at ambient temperature proved optimal (Scheme 1). Thus, for the monosubstituted alkene **2**, chloride **4** was isolated in 82 % yield.[9] The use of the cheaper tetramethyldisiloxane (TMDSO) allows the generation of product as well, albeit in reduced yield (65 %). Similarly, conducting the reaction in the absence of *t*BuOOH under otherwise standard conditions ($Co(BF_4)_2{\cdot}6\,H_2O$ and ligand **6**) decreases the yield to 50 %.[10] Having the two reliable procedures in hand we examined the scope of the hydrochlorination reaction as shown in Table 1.

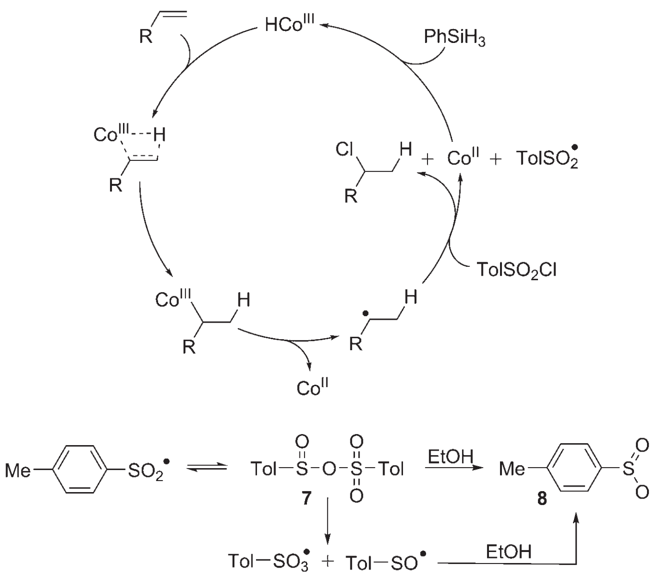
Both protocols were tested, with the optimal results for each substrate shown. All terminal, monosubstituted olefins tested (Table 1, entries 1–8) showed excellent Markovnikov selectivity as linear chlorides were never observed. The in situ formed complex from $Co(BF_4)_2{\cdot}6\,H_2O$ and ligand **6** is generally better for this class of olefins. Simple alkenes with an aromatic ring in the allylic or homoallylic position are very good substrates for the reaction (entries 2 and 1). Styrene derivatives (not shown) unfortunately failed to undergo hydrochlorination under our reaction conditions, although they are substrates in the related hydrocyanation and hydrohydrazination reactions. Thus, the method complements the traditional approach, as styrenes undergo addition by HCl.[2,5] Free alcohols proved to be unreactive; however, when protected as the corresponding silyl or benzyl ethers (entries 3–5), they smoothly undergo hydrochlorination to provide the corresponding products in good yields. The reaction also tolerates ketones (entry 6), amides (entry 7), and esters (entry 11). Interestingly, the monosubstituted alkene with an amide group (entry 7) underwent addition only in the presence of slightly higher loadings of catalyst **5** (8 mol % to obtain full conversion). In the case of 1,1-disubstituted and trisubstituted olefins (entries 9–13) both catalytic systems could be used, providing the tertiary chlorides exclusively. For these substrates, catalyst **5** was slightly more active, as lower catalyst loading could be used and the products were isolated in higher yields. It is important to note, that after completion of the reaction, simple removal of the solvent followed by chromatography on silica gel furnishes the hydrochloride adducts cleanly.

Table 1: Hydrochlorination reaction of olefins according to Scheme 1.[a]

Entry	Alkene	Product	Catalyst (mol %)	Yield [%]
1			**6** (6)	92
2			**6** (10)	94
3			**6** (12)	82
4			**6** (12)	73
5			**6** (12)	76
6			**6** (12)	84
7			**5** (8)	88
8			**5** (5)	67
9			**5** (2)	80
10			**5** (2)	96
11			**5** (2)	93
12			**5**[b] (2)	87
13			**5** (5)	75

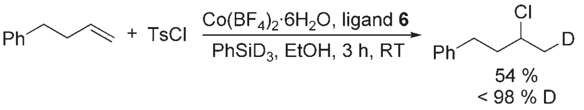
[a] Conditions for reactions with catalyst **5**: alkene (0.5 mmol), TsCl (0.6 mmol), $PhSiH_3$ (0.5 mmol), EtOH (2.5 mL), Ar, 23 °C; conditions for reactions with ligand **6**: $Co(BF_4)_2{\cdot}6\,H_2O$, alkene (0.5 mmol), TsCl (0.6 mmol), *t*BuOOH (30 mol %), $PhSiH_3$ (0.5 mmol), EtOH (2.5 mL), Ar, 23 °C. [b] d.r. = 15:1.

Our working model for the mechanism of this transformation is shown in Scheme 2 and is proposed to involve olefin hydrocobaltation and interception of the organocobalt or derived radical by TsCl. The mechanism parallels that which we proposed and studied in detail for the hydrohydrazination and hydroazidation reactions.[7] The catalytic cycle is initiated by formation of a cobalt–hydride complex (Co^{II} or Co^{III} and silane). This is followed by regioselective olefin hydrocobaltation placing the cobalt atom on the more substituted carbon atom. This would account for the observation that the secondary and tertiary organochlorides from 1,1-di- and tri-substituted alkenes, respectively, are the sole products of the reaction. We have conducted a deuterium-labeling experiment that provides further support for this suggestion. Thus, the reaction of 4-phenylbutene with $PhSiD_3$ under otherwise standard hydrochlorination conditions dis-



Scheme 2. Working model for the mechanism of the hydrochlorination reaction.

played complete deuterium incorporation at the terminal position [Eq. (2)].



(2)

The steps by which the organocobalt intermediate is converted into the chloride product remain unclear, but may very well involve a free-radical intermediate. The reaction of TsCl with the carbon radical produced upon homolysis of C–Co would lead to the chloride product together with a toluenesulfonyl radical. Sulfonyl radicals have been demonstrated to form unstable sulfinylsulfonates (**7**; see Scheme 2), or mixed anhydrides.[11] It has been suggested that these sulfonates collapse to form sulfinyl radicals. However, the fact that we observed the formation of ethyl 4-methylbenzenesulfinate (**8**) as a byproduct of the reaction leads us to propose that it undergoes more rapid attack by EtOH. Regeneration of the cobalt–hydride complex by the action of phenylsilane would complete the catalytic cycle. One might envisage the hydrochlorination of alkenes taking place simply by the action of hydrochloric acid, formed from TsCl with EtOH to produce ethyl sulfonate. However, in a control experiment, we have shown that when the reaction is conducted in the absence of any alkene under otherwise standard conditions, formation of ethyl sulfonate is less than 30% in five hours. Additionally, the fact that silyl-protected substrates (entries 3, 4, 10, and 13) can be used suggests that the concentration of acid remains low throughout the course of the reaction. Ongoing studies are aimed at providing further experimental support for this hypothesis.

In summary, we have reported the hydrochlorination of unactivated alkenes under mild conditions (room temperature, EtOH as solvent) that is tolerant to a range of functional groups. Monosubstituted olefins, which to date are recognized as being a challenging class of substrates for direct addition by HCl, can now be easily converted into the corresponding secondary chlorides using the catalyst system described herein. Importantly, all of the reaction components are commercially available, such as TsCl, $PhSiH_3$, $Co(BF_4)_2{\cdot}6H_2O$, as well as ligand **6** (from Aldrich under the name of SALDIPAC),[12] or can be easily prepared (catalyst **5**). In a broader sense, the use of TsCl with olefins to afford organochlorides lacks precedence; its role as Cl-transfer reagent is intriguing and may have additional applications in other processes.

Experimental Section

General procedure with catalyst **5**: Complex **5** (6 mg, 0.01 mmol, 2 mol%) was dissolved in EtOH (absolute from Merck, 2 mL) at room temperature (RT) under argon. After 2 min, alkene (0.5 mmol) was added followed by TsCl (99% ACROS, 116 mg, 0.6 mmol, 1.2 equiv) and $PhSiH_3$ (98% ACROS, 62 μL, 0.5 mmol, 1.0 equiv). Another portion of EtOH (0.5 mL) was added. The resulting green solution was stirred at RT and the reaction was monitored by thin-layer chromatography (TLC). After completion (3–7 h) the solvent was evaporated and the crude mixture purified by flash chromatography to afford the corresponding chloride.

General procedure with the in situ generated catalyst: $Co(BF_4)_2{\cdot}6H_2O$ (10 mg, 0.03 mmol, 6 mol%) and ligand **6** (14 mg, 0.03 mmol, 6 mol%) were dissolved in EtOH (2 mL) at RT under argon. After 2 min alkene (0.5 mmol) was added followed by TsCl (99% ACROS, 116 mg, 0.6 mmol, 1.2 equiv) and *t*BuOOH (5.5 M solution in decane, 25 μL, 0.28 equiv). Finally $PhSiH_3$ (98% ACROS, 62 μL, 0.5 mmol, 1.0 equiv) was added and another portion of EtOH (0.5 mL). The resulting green solution was stirred at RT and the reaction was monitored by TLC. After completion (3–7 h) the solvent was evaporated and the crude mixture purified by flash chromatography to afford the corresponding chloride.

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[1] a) F. C. Whitmore, F. Johnston, *J. Am. Chem. Soc.* **1933**, *55*, 5020–5022; b) L. Schmerling, *J. Am. Chem. Soc.* **1946**, *68*, 195–196; c) J. K. Stille, F. M. Sonnenberg, T. H. Kinstle, *J. Am. Chem. Soc.* **1966**, *88*, 4922–4925; d) R. C. Fahey, C. A. McPherson, *J. Am. Chem. Soc.* **1971**, *93*, 2445–2453; e) K. B. Becker, C. A. Grob, *Synthesis* **1973**, 789–790; f) K. B. Becker, C. A. Grob, *Helv. Chim. Acta* **1973**, *56*, 2723–2732.

[2] a) M. J. S. Dewar, R. C. Fahey, *J. Am. Chem. Soc.* **1963**, *85*, 2245–2248; b) H. C. Brown, M.-H. Rei, *J. Org. Chem.* **1966**, *31*, 1090–1093.

[3] a) J. P. Kennedy, S. Sivaram, *J. Org. Chem.* **1973**, *38*, 2262–2264; b) P. J. Kropp, K. A. Daus, S. D. Crawford, M. W. Tubergen, K. D. Kepler, S. L. Craig, V. P. Wilson, *J. Am. Chem. Soc.* **1990**, *112*, 7433–7434; c) H. Alper, Y. Huang, *Organometallics* **1991**, *10*, 1665–1671.

[4] a) P. J. Kropp, K. A. Daus, M. W. Tubergen, K. D. Kepler, V. P. Wilson, S. L. Craig, M. M. Baillargeon, G. W. Breton, *J. Am. Chem. Soc.* **1993**, *115*, 3071–3079; b) P. Boudjouk, B.-K. Kim, B.-H. Han, *Synth. Commun.* **1996**, *26*, 3479–3484; c) V. K. Yadav, K. G. Babu, *Eur. J. Org. Chem.* **2005**, 452–456.

[5] S. M. Podhajsky, M. S. Sigman, *Organometallics* **2007**, *26*, 5680–5686.

[6] a) J. Waser, E. M. Carreira, *J. Am. Chem. Soc.* **2004**, *126*, 5676–5677; b) J. Waser, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 4191–4194; *Angew. Chem. Int. Ed.* **2004**, *43*, 4099–4102; c) J. Waser, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 8294–8295; d) J. Waser, J. C. González-Gómez, H. Nambu, P. Huber, E. M. Carreira, *Org. Lett.* **2005**, *7*, 4249–4252.

[7] J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712.

[8] B. Gaspar, E. M. Carreira, *Angew. Chem.* **2007**, *119*, 4603–4606; *Angew. Chem. Int. Ed.* **2007**, *46*, 4519–4522.

[9] It is important to note that in the case of alkene **4** the reaction should be stopped immediately after consumption of the starting material, as longer reaction times lead to decomposition and lower yields.

[10] For a discussion on the effect of peroxides on the reaction rate in oxygenation reactions, see: T. Tokuyasu, S. Kunikawa, A. Masuyama, M, Nojima, *Org. Lett.* **2002**, *4*, 3595–3598.

[11] J. E. Bennett, G. Brunton, B. C. Gilbert, P. E. Whittall, *J. Chem. Soc. Perkin Trans. 2* **1988**, 1359–1364.

[12] SALDIPAC, Aldrich catalog number 676551; *Aldrichimica acta* **2007**, *40*, 1, page 6.