Iron Carbene Catalysis

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Catalytic Activation of Diazo Compounds Using Electron-Rich, Defined Iron Complexes for Carbene-Transfer Reactions

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The activation of diazo compounds by nitrogen extrusion in the presence of transition-metal complexes is a convenient method for the transfer of a carbene to an organic substrate in, for example, [2+1] cycloadditions with olefins[1] or carbonyl compound[2] to give three-membered-ring compounds, or in reactions with electron-rich heteroatoms like sulfur,[3] phosphorus,[4] and nitrogen[5] to generate ylides.[6] In general, these types of reactions are catalyzed by oxidized transition-metal complexes based upon copper,[1,7] rhodium,[5a–d] ruthenium,[8] palladium,[9] cobalt,[10] iron,[4,11] and silver.[12] In the initial step the metal center is reduced by nucleophilic addition of the diazo compound. The subsequent back-donation of an electron from the metal to the carbon atom with concomittant release of nitrogen results in the formation of the metal–carbon double bond [Eq. (1) in Figure 1].

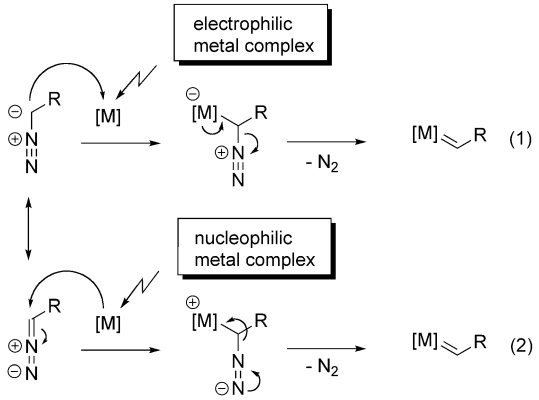


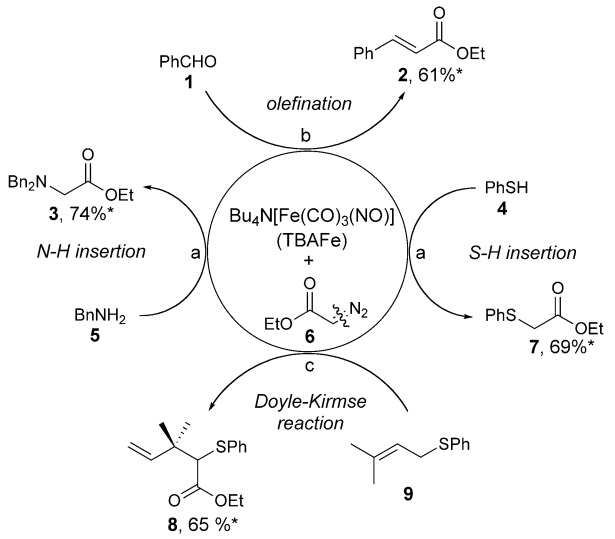
Figure 1. Mechanistic model for the decomposition of diazo compounds by electrophilic or nucleophilic metal catalysts.

In contrast, the corresponding activation of stabilized, electron-poor diazo compounds by nucleophilic and hence electron-rich transition-metal complexes is unprecented. From a mechanistic point of view the metal center would add into the C=N bond of the diazo compounds followed by an electron back-donation with release of nitrogen and formation of the metal–carbon double bond [Eq. (2), Figure 1].[13] With respect to the oxidation state of the metal center both mechanistic manifolds are redox-neutral; however, the latter mechanism might favor the undesired carbene dimerization to the corresponding olefins.

We were wondering whether the electron-rich ferrate complex $Bu_4N[Fe(CO)_3(NO)]$ (TBAFe), in which the metal center has a formal oxidation state of −II and which has been investigated in detail by us and others over the past years,[14] might be able to activate diazo compounds for carbene-transfer reactions. Herein we report the successful realization of this concept in various catalytic transformations including Wittig-type olefinations,[15] the insertion into heteroatom–hydrogen bonds,[16] and the Doyle–Kirmse reaction.[17]

Since to the best of our knowledge the activation of diazo compounds by reduced metal catalysts has not been reported, we initiated our studies by investigating the carbene transfer using ethyl diazoacetate (**6**, EDA) as the electrophilic carbene precursor in different model reactions. Apart from its electronic properties, which could result in an increased reactivity toward electron-rich metal complexes, this diazo compound is stable and commercially available in pure form. Gratifyingly, a system consisting of catalytic amounts of TBAFe and stoichiometric amounts of **6** showed good reactivity in 1,2-dichloroethane (Scheme 1).

Both the insertion into S–H and N–H bonds as well as the transfer of the carbenoide to electron-rich heteroatoms with intermediate formation of an ylide (olefination[18,19] and Doyle–Kirmse reaction) were accomplished under almost



Scheme 1. TBAFe-catalyzed carbene-transfer reactions. Reaction conditions: a) 10 mol% TBAFe, 1.2 equiv **6**, 1,2-dichloroethane, 60°C, 18 h; b) 10 mol% TBAFe, 1.2 equiv **6**, 1.5 equiv $AsPh_3$, 1,2-dichloroethane, 60°C, 18 h; c) 10 mol% TBAFe, 1.2 equiv **6**, 1,2-dichloroethane, 60°C, 2 h. *: yield of isolated product.

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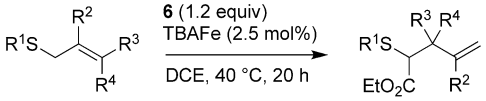
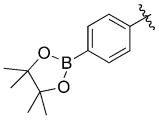
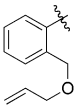
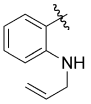
identical reaction conditions. Since the Doyle–Kirmse reaction proved to be the highest yielding model reaction, further optimizations concentrated on variation of solvent, temperature, ligand effects, and catalyst loadings.

The subsequent optimization studies indicated that a decrease in the temperature down to 40 °C and catalyst concentration down to only 2.5 mol % is possible even in the absence of ligands. Furthermore 1,2-dichloroethane (DCE) proved to be the solvent of choice.[20] A variety of alkyl/arylthioethers were subjected to the optimized reaction conditions using **6** as the carbene precursor (Table 1).

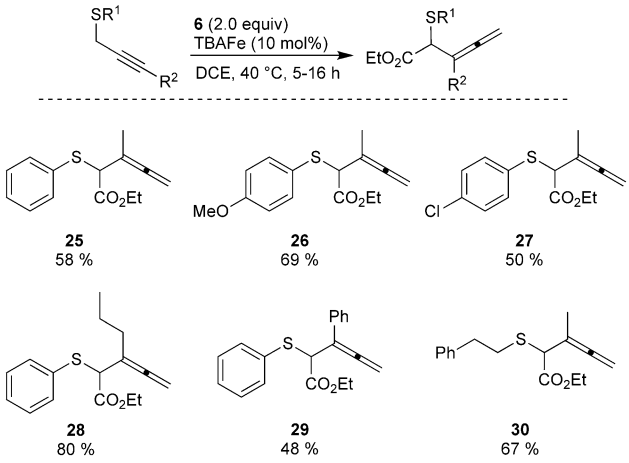
Table 1: The iron-catalyzed Doyle–Kirmse reaction.



Entry[a]	R^1	R^2	R^3	R^4	Prod.	Yield [%][b]
1	Ph	H	H	H	**10**	88
2	Ph	H	Me	H	**11**	76
3[c]	Ph	H	Me	Me	**8**	77
4[d]	Ph	Me	H	H	**12**	63
5[c]	Ph	H	Ph	H	**13**	70
6[c]	*p*-ClC_6H_4	H	Me	Me	**14**	81
7	*p*-$MeOC_6H_4$	H	Me	Me	**15**	90
8	*p*-MeC_6H_4	H	Me	Me	**16**	68
9[d]	Bn	H	Me	Me	**17**	69
10[c]	*n*Hex	H	Me	Me	**18**	92
11[c]		H	H	H	**19**	65
12[c]		H	H	H	**20**	51
13[c]		H	H	H	**21**	49
14[c]		H	H	H	**22**	74
15		H	H	H	**23**	75
16		H	H	H	**24**	76

[a] All reactions were performed on a 1 mmol scale in 1,2-dichloroethane (1 mL) under a N_2 atmosphere at 40 °C. [b] Yields of isolated products. [c] $T = 60$ °C. [d] $T = 80$ °C.

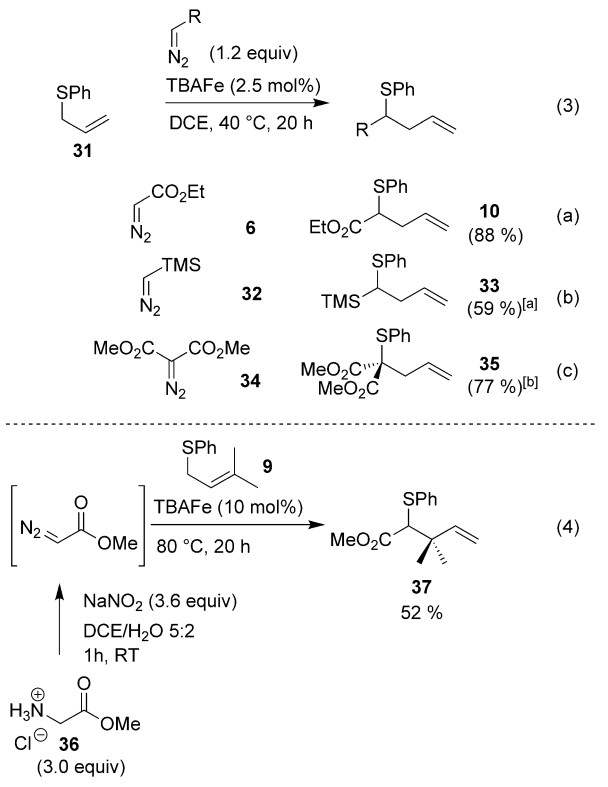
The reaction shows a remarkable scope. The desired rearrangement products were obtained in good to excellent yields in the presence of only a slight excess of **6**. Base-labile functional groups like boronates (entry 11, Table 1) or functional groups that are reactive toward carbene-transfer reactions (e.g. alcohols, amines, olefins, entries 11–16, Table 1) proved to be compatible with the reaction conditions. Byproducts indicative of an undesired side reaction were not observed. This observation might be explained by the lower reactivity of these groups as observed in our initial model studies (Scheme 1).



Scheme 2. Iron-catalyzed Doyle–Kirmse reaction of propargyl sulfides.

Further investigations showed that the reaction conditions are applicable for propargyl sulfides (Scheme 2). Various propargylic thioethers were transformed into the corresponding allenes in good to excellent yields using slightly modified reaction conditions.

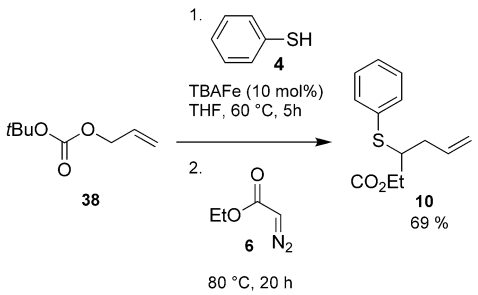
Finally we investigated the scope with respect to the diazo compounds. The catalytic systems proved to be robust. Electron-rich as well as 1,1-disubstituted diazo compounds were successfully employed in the Doyle–Kirmse reaction [Eq. (3), Scheme 3]. However, the catalyst concentration, stoichiometry, and/or reaction temperature have to be



Scheme 3. Iron-catalyzed Doyle–Kirmse reaction of various diazo compounds. [a] $T = 80$ °C. [b] $T = 120$ °C; catalyst concentration: 10 mol %.

adjusted for the respective reagents. The preparation and handling of diazo compounds certainly represents a serious limitation from a preparative point of view. Based upon the recent work carried out in the Carreira group,[21] a one-pot procedure consisting of in situ generation of the active diazo compound and subsequent Doyle–Kirmse reaction, was realized [Eq. (4), Scheme 3]. The catalytic transformation can be performed in a two-phase mixture of water and 1,2-dichloroethane without any intermediate purification steps. The desired product **37** was obtained in moderate (non-optimized) yield. This result underlines the extraordinary stability of the catalyst.

Recently we reported that TBAFe is able to catalyze the regioselective allylation of thiols in the absence of any ligand.[13f] With regard to the results reported above, we speculated that we could employ this complex in a sequential sulfenylation/Doyle–Kirmse reaction. Treatment of allylic carbonate **38** with thiophenol and subsequent addition of **6** to the reaction mixture allowed for the successful realization of this concept. The corresponding ethyl α-mercapto-α-allyl-acetate (**10**) was obtained in good yield (Scheme 4).



Scheme 4. Sequential iron-catalyzed allylic sulfenylation and Doyle–Kirmse reaction.

We have shown that electron-rich iron complexes like $Bu_4N[Fe(CO)_3(NO)]$ (TBAFe), in which the metal center has a formal oxidation state of −II, activate diazo compounds for carbene-transfer reactions. In the presence of catalytic amounts of the iron complex, an insertion into heteroatom–hydrogen bonds, an olefination of carbonyl compounds, and a Doyle–Kirmse reaction were realized even in the absence of any ligand. The latter transformation displays a broad functional-group tolerance. The mild reaction conditions and the stoichiometric use of the reagent are interesting with regard to possible synthetic applications. The remarkable stability of the catalyst was demonstrated by the in situ generation of the diazo compound and a sequential allylic substitution/Doyle–Kirmse reaction. These results represent the starting point for the preparation of iron–carbene complexes which we will examined in our future research.

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[19] We agree with one of the reviewers that olefinations using stoichiometric amounts of $AsPh_3$ are not contemporary . The olefination shown in this article was meant to be a "proof-of-concept" example and not necessarily a new synthetic method. The exploration of more environmentally benign olefination is currently a research focus. The olefination using catalytic amounts of $AsPh_3$ (Ref. [18]), however, exemplifies the potential of these neutral olefinations.

[20] For details see the Supporting Information.

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