Allylic Alkylation

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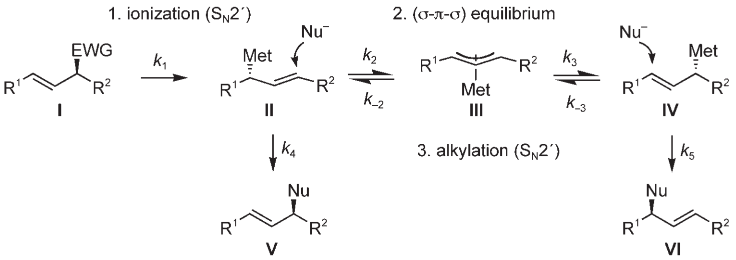
A Highly Regioselective Salt-Free Iron-Catalyzed Allylic Alkylation**

*Bernd Plietker**

Transition-metal-catalyzed reactions belong to the most important tools in synthetic organic chemistry. Over the past 30 years the productive collaboration between organic and inorganic chemists has led to a dynamic evolution in this field and, as a consequence, to the development of a variety of new transformations.[1] Apart from the invention of new reactions, the use of only small amounts of a catalyst is advantageous with regard to environmental aspects. Although the amount of catalyst employed is usually very low the high price of these compounds often prevents their application on a large scale. Hence, the search for new catalysts based on inexpensive nontoxic metals such as iron has gained increasing attention in the past years.[2]

Allylic alkylation is among the most successful catalytic C–C bond formations in organic chemistry.[3] A variety of transition metals can be used for the selective reaction between a C nucleophile and allylic activated substrates. Detailed investigations, especially in the field of palladium catalysis, have made allylic alkylation a versatile synthetic tool in preparative organic chemistry.[4] Although palladium is the predominant metal in this field, various procedures involving ruthenium,[5] iridium,[6] nickel,[7] tungsten,[8] copper,[9] or molybdenum catalysts[10] have been published. In most cases, intermediate π-allyl metal complexes are formed that allow asymmetric allylic alkylation through addition of chiral ligands. However, the reaction of unsymmetrically substituted substrates often leads to the formation of regioisomers.[11,12]

To date, a catalytic regioselective allylic alkylation in which the new C–C bond is formed at the carbon atom that bears the leaving group in the starting material was only observed in the presence of rhodium catalysts by the groups of Evans[13] and Martin.[14] To favor such a reaction, a fast alkylation of **II** (k_1,$k_4 \gg k_2$,k_3; Scheme 1) might prevent the formation of the undesired π-allyl metal intermediate **III**, thus leading to the observed regioselective C–C bond formation in the product **V** (σ-allyl metal mechanism).[13a]



Scheme 1. Allylic alkylation through σ-allyl (k_1,$k_4 \gg k_2$,k_3) or π-allyl metal mechanism (k_2,$k_3 \gg k_4$,k_5). EWG = electron-withdrawing group.

Roustan et al.[15] and Xu and Zhou[16] reported a regioselective, allylic alkylation in the presence of the formal Fe^{-II} complex [Bu$_4$N][Fe(CO)$_3$(NO)]. Although from an economical and ecological point of view this catalyst represents an interesting alternative to the commonly used transition-metal complexes, this catalytic process was not studied further owing to the high catalyst loading (25 mol %) and the need for a toxic CO atmosphere.[17,18]

Within the course of the synthesis of a natural product, we sought a regioselective allylic alkylation method in which the new C–C bond is formed at the carbon atom that bears the nucleofuge in the starting material. Although almost ignored, C–C bond formation in the presence of a Fe^{-II} complex appeared remarkable to us with regard to both practicability and stability of the catalyst.[14,15] Herein we summarize the results of our investigations based on the pioneering work of Roustan and Xu that have led to the development of an efficient, regioselective, salt-free, iron-catalyzed allylic alkylation.[19] The scope of the reaction for different pronucleophiles and allyl carbonates is discussed below.[20]

The primary goal of our initial investigations in this field was the replacement of the toxic CO atmosphere. The low conversion in the absence of CO indicated a deactivation of the catalyst within the first catalytic cycle (Table 1, entry 1). Based on the assumption that the CO atmosphere should suppress deactivating ligand-exchange processes at the metal center, various ligands were tested in order to replace the CO atmosphere (Table 1). A probable coordination at the metal center could maintain the catalyst activity, thus taking over the function of the CO atmosphere. Surprisingly, triphenylphosphane, a monodentate basic ligand, showed optimum results (Table 1, entry 3).[21] Furthermore, the separate deprotonation of the pronucleophile proved to be unnecessary, thus allowing a salt-free reaction procedure.

Subsequent investigations on the influence of the carbonate structure indicated an isobutyl carbonate to be beneficial for the reaction. The change in the carbonate structure improved the yield significantly from 41% to 68%. A subsequent optimization of the solvent indicated that strongly coordinating solvents such as *N*,*N*-dimethylformamide increase the reactivity of the catalyst (Table 2, entry 8).[22] The moderate regioselectivity in the presence of acetonitrile is surprising and suggests an alternative π-allyl metal mechanism (Table 2, entry 7). Investigations on the mechanism are

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[*] Priv.-Doz. Dr. B. Plietker
Organische Chemie II, FB Chemie
Universität Dortmund
Otto-Hahn-Strasse 6, 44221 Dortmund (Germany)
Fax: (+49) 231-755-3884
E-mail: bernd.plietker@uni-dortmund.de

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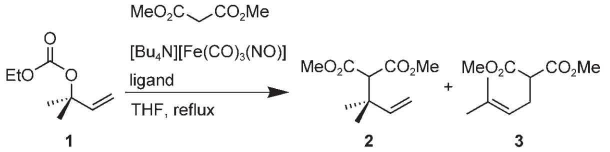
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Ligand effect in the allylic alkylation of **1**.[a]



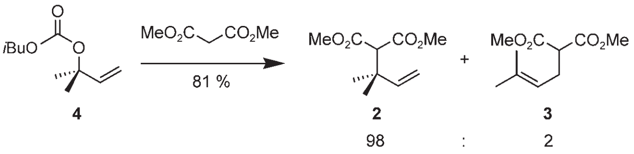
Entry	Ligand	**2/3**[b]	Conversion [%][c]
1	–	n.d.[d]	8
2	pyridine	n.d.	6
3	PPh_3	96:4	41
4	PBu_3	92:8	26
5	$P(OEt)_3$	n.d.	12
6	dppe[e]	n.d.	8
7	dppp[e]	n.d.	11
8	dppf[e]	n.d.	13

[a] All reactions were performed on a 1-mmol scale under argon in the presence of the Fe catalyst (10 mol%), ligand (10 mol%), and pronucleophile (2 equiv) in absolute THF (5 mL) and stopped after 12 h. [b] Determined by GC. [c] Determined by GC relative to undecane as internal standard. [d] Not determined. [e] dppe = Ethane-1,2-diylbis(diphenylphosphane), dppp = propane-1,3-diylbis(diphenylphosphane), dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

Table 2: Solvent effect in the allylic alkylation.[a]

Entry	Solvent	**2/3**[b]	Conversion [%][c]
1	THF	96:4	68
2	DME[d]	92:8	43
3	acetone	n.d.	12
4	CH_2Cl_2	n.d.	–
5	toluene	97:3	39
6	DMSO	96:4	46
7	CH_3CN	58:42	60
8	DMF[d]	98:2	95
9	NMP[d]	97:3	82

[a] All reaction were carried out in the presence of the Fe catalyst (10 mol%) and PPh_3 under otherwise identical conditions as described in Table 1. [b] Determined by GC. [c] Determined by GC relative to undecane as internal standard.



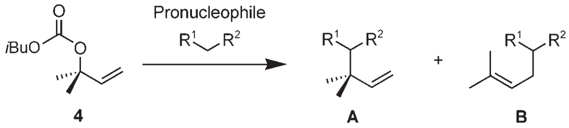
Scheme 2. Iron-catalyzed allylic alkylation. Reagents and conditions: substrate (1 mmol), pronucleophile (2 mmol), $[Bu_4N][Fe(CO)_3(NO)]$ (2.5 mol%), PPh_3 (3 mol%), DMF (1 mL), 80 °C, 24 h.

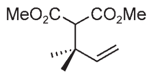
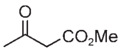
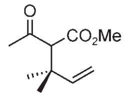
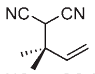
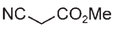
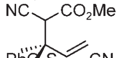
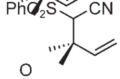
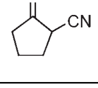
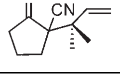
currently being carried out in our laboratories. An increase in the substrate concentration from 0.2 to 1 molL^{-1} allowed a further decrease in the catalyst loading to as little as 2.5 mol% while maintaining the regioselectivity. The optimized conditions are shown in Scheme 2.

The iron-catalyzed allylic alkylation is applicable to a variety of different C nucleophiles (Table 3). Nitrile-containing pronucleophiles proved to be most reactive. The presence of only one CN group decreases the reaction time significantly (Table 3, entries 3–6). The formation of two adjacent quaternary carbon centers in the presence of the iron catalyst proceeds in good yields (Table 3, entry 6). However, this C−C bond formation is not as regioselective as the formation of only one quaternary center. Apparently, the steric repulsion between the substituents at the allyl fragment and the nucleophile leads to a lower selectivity. However, the branched product is still the major product.

The iron-catalyzed allylic alkylation is applicable to a variety of differently substituted allyl carbonates (Table 4). In

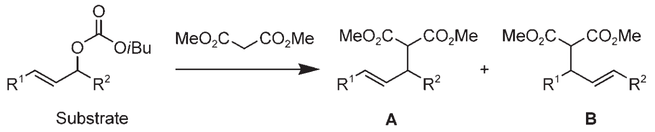
Table 3: Iron-catalyzed allylic alkylation of different pronucleophiles.[a]

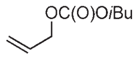
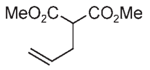
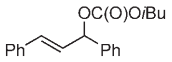
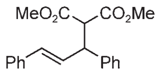
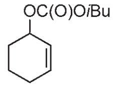
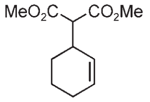
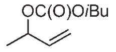
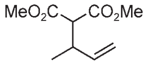
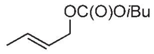
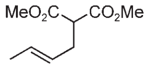
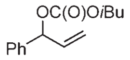
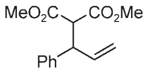
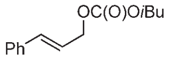
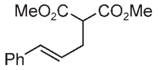
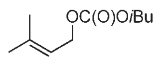
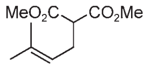
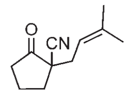


Entry	Pronucleophile		Product **A**		*t* [h]	**A/B**[b]	Yield [%][c]
1		**5**		**2**	24	98:2	81
2		**6**		**7**	24	96:4	71
3		**8**		**9**	12	92:8	74
4		**10**		**11**	12	94:6	79
5		**12**		**13**	12	94:6	92
6		**14**		**15**	12	87:13	81

[a] All reactions were carried out on a 1-mmol scale in the presence of the Fe catalyst (2.5 mol%), PPh_3 (3 mol%), and the pronucleophile (2 equiv) in absolute DMF (1 mL) at 80 °C. [b] Determined by GC. [c] Yield of both regioisomers after isolation.

Table 4: Iron-catalyzed allylic alkylation of various carbonates.[a]

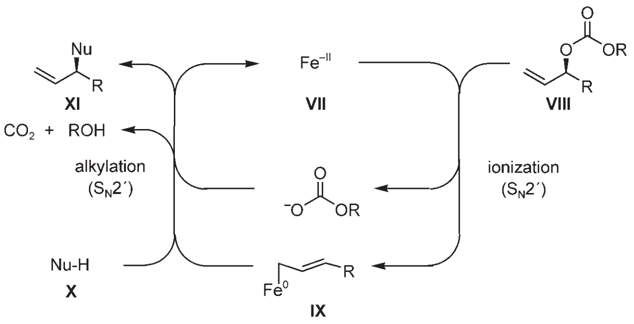


Entry	Substrate		Product **A**		*t* [h]	**A**:**B**[b]	Yield [%][c]
1		**16**		**17**	12	93:7	84
2		**18**		**19**	48	–	53
3		**20**		**21**	48	–	69
4		**22**		**23**	24	98:2	78
5		**24**		**25**	36	96:4	76
6		**26**		**27**	24	98:2	78
7		**28**		**29**	48	92:8	56
8		**30**		**3**	48	93:7	61
9		**30**		**31**	24	84:16	65

[a] All reactions were performed as indicated in Table 3. [b] Determined by GC. [c] Combined yield of both regioisomers after isolation.

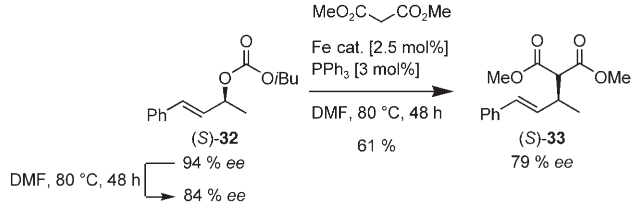
every case the substitution takes place at the carbon atom that bears the original leaving group. The introduction of further olefin substituents has a significant influence on the course of the reaction. More substituents lead to longer reaction times.[23] However, we were pleased to find that the regioselectivity is not influenced (Table 4). Whereas aliphatic substituents solely prolong the reaction times, a phenyl substituent at C3 of the allyl fragment leads to a significantly lower yield (Table 4, entries 2 and 7). The regioselectivity of the reaction is defined exclusively by the substitution pattern of the allyl carbonate (Table 4, entries 4/5 and 6/7). In contrast, the nature of the pronucleophile does not influence the regioselectivity (Table 3, entry 1 and Table 4, entry 8; Table 3, entry 6 and Table 4, entry 9).

From the observed high regioselectivity in the alkylation it can be concluded that, in contrast to most common transition-metal-catalyzed allylic alkylations, no η^3-allyl intermediate is formed in this reaction. A selective double S_N2' addition both of the metal **VII** (Scheme 3) in the first and of the nucleophile **X** in the second step allows the observed high regioselectivity. An oxidative addition through an S_N2 mechanism appears to be unlikely as both reaction time and conversion rate in the alkylation of primary allyl carbonates clearly depends on the substitution pattern at C3 of the allyl fragment (Table 4, entries 1, 5, and 9).[23] A preliminary mechanistic proposal is shown in Scheme 3.



Scheme 3. Postulated catalytic cycle for the iron-catalyzed allylic alkylation.[24]

The proposed mechanism has stereochemical consequences. If indeed only a σ-allyl metal species such as **IX** is formed in situ, the allylic alkylation of enantiomerically enriched carbonates should lead to the formation of enantiomerically and regioisomerically enriched substitution products with retention of the configuration. To test this hypothesis (*S*)-allyl carbonate **33** was subjected to the alkylation conditions. The enantiomeric ratios of the starting material and of the product were analyzed by means of chiral HPLC (Scheme 4). The enantiomeric excess decreased to a certain extent; however, the *S*-configured malonic ester derivative **34** was formed as the main product. The lower *ee* values are probably the result of epimerization of the starting material under the reaction conditions. This hypothesis was proven by a control experiment in which (*S*)-**33** was subjected to the reaction conditions in the absence of the iron catalyst. After 48 h a decrease in the enantiopurity to 83 % *ee* was observed. Hence, at the current state of research such an epimerization event might be responsible for the observed loss in enantioselectivity. However, this test reaction serves as a first indication that a σ-allyl metal mechanism takes place in the iron-catalyzed allylic alkylation.



Scheme 4. Iron-catalyzed allylic alkylation of enantiopure carbonate (*S*)-**33**.

In summary, we have described an efficient, salt-free, regioselective iron-catalyzed allylic alkylation of allyl carbonates. The addition of triphenylphosphane led to a significant increase in reactivity of the [Fe(CO)$_5$]-derived stable iron(−II) complex [Bu$_4$N][Fe(CO)$_3$(NO)]. In the presence of the catalyst (2.5 mol %) and PPh$_3$ (3 mol %) a variety of different allyl carbonates and pronucleophiles were coupled in good to excellent yields. The use of a carbonate as leaving group avoids a separate deprotonation of the pronucleophile by external bases. Apart from the possible salt-free reaction course, a fact that is especially attractive for applications on a preparative scale, the high regioselectivity of the alkylation is remarkable. The new C−C bond is formed selectively at the carbon atom in the allyl fragment that bears the leaving group in the starting material. Comparable high regioselectivities were previously only observed in the presence of rhodium catalysts. Further investigations on the mechanism, stereo- and regioselectivity aspects, and scope and limitations are currently underway in our laboratories.

Experimental Section

2: A 10-mL Schlenk tube was charged with the iron catalyst (10.6 mg, 0.025 mmol, 2.5 mol %) and PPh$_3$ (7.3 mg, 0.03 mmol, 3 mol %), which were then dissolved under argon in dry DMF (1 mL) and heated to 80 °C for 30 min. The mixture was cooled to room temperature, and the allyl carbonate **4** (186 mg, 1 mmol) and dimethyl malonate (232 mg, 2 mmol) were then added. The reaction mixture was heated in the sealed Schlenk tube for 24 h at 80 °C. The mixture was cooled to room temperature, and dichloromethane (20 mL) was then added. The organic layer was extracted with water (2 × 10 mL) and dried over a mixture of Na$_2$SO$_4$ and charcoal (1:1; ≈5 g). After filtration and evaporation of the solvent a pale yellow liquid was obtained which was purified by flash column chromatography (isohexane/diethyl ether, 5:1). Yield: 162 mg (0.81 mmol, 81 %).

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Keywords: alkylation · carboxylic acids · iron · nucleophiles · regioselectivity

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[24] The presented mechanism, including the molecular structures, represents a model. Detailed spectroscopic investigations on the structure of the active catalyst as well as on reactive intermediates are currently underway in our laboratories.