Homogeneous Catalysis

DOI: 10.1002/anie.200602261

Regioselective Iron-Catalyzed Allylic Amination**

*Bernd Plietker**

Catalysis in the presence of inexpensive and nontoxic metals has gained increasing attention in chemical research within the past years. In particular, iron complexes proved to be efficient and selective catalysts for a variety of transformations.[1] With regard to the importance of allylic substitutions in organic synthesis[2] the development of an iron-catalyzed protocol appeared to be a useful extension of the existing methodologies. Recently, we presented the first regioselective, salt-free, iron-catalyzed allylic alkylation of allyl carbonates.[3] In this reaction a new C–C bond is formed with retention of the configuration at the carbon atom that was substituted by the leaving group in the starting material. Aiming to broaden the scope of the reaction and to gain further information on stability and reactivity of the iron catalyst $[Bu_4N][Fe(CO)_3(NO)]$, we further developed this reaction into an iron-catalyzed, allylic amination. Such a reaction has not been developed until now.

Various transition metals are known to catalyze the allylic amination.[4] The classical version in the presence of Pd catalysts, however, exhibits a lack of regioselectivity. In general, the product resulting from an attack of the nucleophile at the sterically less encumbered allyl terminus is formed predominantly. The preparation of higher-substituted, branched amines can be realized in the presence of Ir[5] or Ru catalysts.[6] However, in all of these protocols the substitution pattern in the π-allyl metal intermediate determines the regioselective course of the reaction. The Rh-catalyzed allylic amination on the other hand might be regarded as a complementary procedure.[7] In this reaction both the regio- and stereoselectivity are solely determined by the constitution of the starting material.[8] The new C–N bond is formed selectively at the carbon atom that was substituted by the leaving group in the starting material.

[*] 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

[**] Financial support from Prof. Dr. N. Krause, the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, the Dr.-Otto-Röhm-Gedächtnisstiftung, and the Fonds zur Förderung des wissenschaftlichen Nachwuchses im Fachbereich Chemie der Universität Dortmund is gratefully acknowledged.

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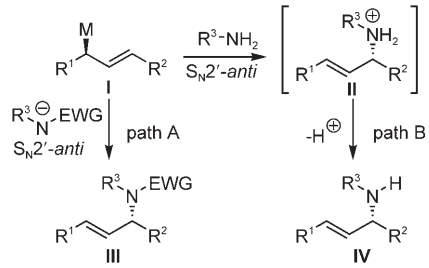
Although allylic substitutions are formally related to C or N nucleophiles, the direct nucleophilicity[9] of the nitrogen atom causes significant mechanistic differences (Scheme 1).



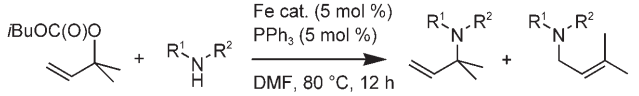
Scheme 1. Mechanistic dichotomy in allylic aminations. EWG = electron-withdrawing group.

Similar to the C nucleophiles, electron-poor secondary amines have to be deprotonated separately or in situ prior to the allylic substitution and then treated with an allyl metal species **I** (Scheme 1, path A). The low tendency of these nucleophiles and the resulting product **III** to coordinate to the metal center is advantageous for the reaction. Similar processes often lead to catalyst inhibition. Electron-rich primary or secondary amines on the other hand can coordinate to a metal center but offer the possibility to act as a direct nucleophile[9] in the reaction with allyl metal species like **I** (Scheme 1, path B). Upon substitution of the metal center, an ammonium cation **II** is formed which is deprotonated in the final step of the mechanism.

Since no iron-catalyzed allyic amination has been described in the literature so far,[10] the similarity of the allylic amination using electron-poor secondary amines (Scheme 1, path A) with the allylic alkylation motivated us to apply this amine class in initial screening experiments (Table 1, entries 1–4). However, the conversion using this nucleophile class was very low. Moreover, a brown solid was formed during the reaction, which indicated probable catalyst decomposition.

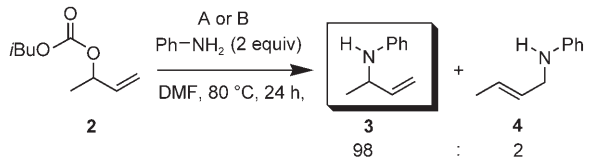
The reaction in the presence of primary amines on the other hand (Scheme 1, path B) furnished the desired allyl amine with a high degree of regioselectivity in favor of the *ipso*-substitution product (Table 1, entry 8). A transfer of these results to the amination of less-substituted allyl carbonates, however, proved to be difficult (Scheme 2).[11]

Table 1: Development of the allylic alkylation of amines.



Entry	R^1	R^2	A/B[a]	Conv. [%][a]
1	Ph	Ts	n.d.[b]	8
2	Ph	Ms	n.d.[b]	12
3	Ph	Ac	n.d.[b]	–
4	*n*Bu	Ts	n.d.[b]	–
5	*n*Pr	*n*Pr	n.d.[b]	–
6	*n*Bu	H	n.d.[b]	12
7	*t*Bu	H	96:4	23
8	Ph	H	97:3	67

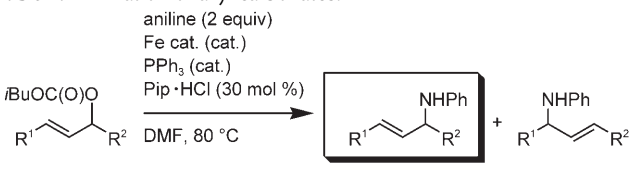
[a] According to GC integration. [b] Not determined. Ts = *p*-toluenesulfonyl, Ms = methanesulfonyl, Ac = acetyl.

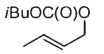
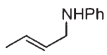
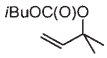
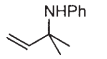
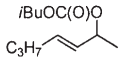
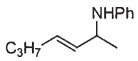
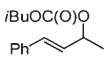
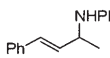


Scheme 2. Iron-catalyzed allylic amination. Conditions: A) Fe cat. (5 mol%), PPh_3 (5 mol%), 1 M, 36% yield; B) Fe cat. (5 mol%), PPh_3 (5 mol%), Pip·HCl (30 mol%), 10 M, 84% yield.

Again, significant catalyst decomposition was observed. This undesired side effect was retarded upon addition of a catalytic amount of piperidinium chloride (Pip·HCl) as a buffer. This addition in combination with an increase in the substrate concentration led to a significant increase in the conversion (Scheme 2), thus allowing for the regioselective amination of primary and secondary allyl carbonates in good yield (Table 2).

Table 2: Amination of allyl carbonates.[a]

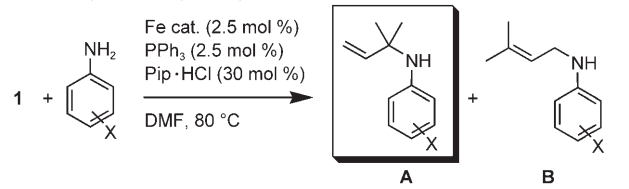


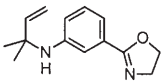
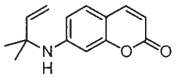
Entry	Carbonate	Product	*t* [h][b]	Yield [%][c,d]
1	 **5**	 **4**	48 (5)	69 (97:3)
2	 **1**	 **6**	6 (2.5)	87 (98:2)
3	 **7**	 **8**	48 (5)	61 (97:3)
4	 **9**	 **10**	24 (5)	62 (96:4)
5	 **11**	 **12**	24 (5)	47 (97:3)

[a] All reactions were performed on a 1-mmol scale. [b] Amount of catalyst in mol% is given in brackets. [c] Yield of isolated product. [d] Regioselectivity of the crude product according to GC integration is given in brackets.

In all cases the new C–N bond is formed with very high selectivity at the carbon atom that was substituted by the leaving group in the starting material. However, both reaction time and yield strongly depend on the substitution pattern of the allyl carbonate: the more highly substituted the double bond the slower the reaction proceeds. Whereas monosubstituted olefins are efficiently aminated, the introduction of one more olefinic substituent leads to a significant increase in the reaction time (**2** vs. **7**; Table 2, entry 3).[12] Furthermore, tertiary allyl carbonates are significantly more reactive compared to primary or secondary carbonates (**1**, **2**, and **5**; Table 2). Both steric and electronic effects might account for this finding. Gratifyingly, the longer reaction times had no impact on the regioselectivity of the reactions.

Table 3: Allylation of primary anilines.[a]



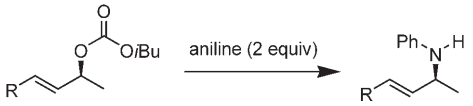
Entry	Product	*t* [h]	Yield [%][b,c]
1	**13** (X = *m*-CH_3)	6	85 (97:3)
2	**14** (X = *p*-CH_3)	6	87 (98:2)
3	**15** (X = *m*-OCH_3)	12	87 (97:3)
4	**16** (X = *p*-OCH_3)	12	82 (98:2)
5	**17** (X = *m*-Cl)	15	71 (96:4)
6	**18** (X = 3,5-CH_3)	6	89 (97:3)
7	 **19**	6	67 (97:3)
8	 **20**	6	93 (97:3)

[a] All reactions were performed on a 1-mmol scale. [b] Yield of isolated product. [c] Regioselectivity of the crude product according to GC integration is given in brackets.

Various aniline derivatives are regioselectively allylated under the optimized reaction conditions (Table 3). Chloride, ether, or ester functionalities are tolerated. Even the presence of strongly coordinating functional groups such as the oxazolidinone in **19** does not lead to a reduction of the catalytic activity. However, the reaction time depends strongly on the nucleophilicity of the nitrogen atom. Electron-poor anilines are allylated more slowly, albeit with the same high degree of regioselectivity, compared to the electron-rich derivatives. Whereas *para*- or *meta*-substituted anilines are efficiently transformed into the corresponding products, a substituent in the *ortho* position inhibits the reaction.

As for the iron-catalyzed allylic alkylation, we envisioned a mechanism involving a σ-allyl metal intermediate as the reason for the observed high regioselectivity. If a stereospecific double S_N2'-*anti* mechanism takes place, the use of enantiomerically pure allyl carbonates should furnish the corresponding amines with retention of the configuration. Indeed, the allylic amination of (*S*)-**9** occurrs with almost complete chirality transfer and retention of the configuration to give amine (*S*)-**10** (Table 4, entries 1–3). This result

Table 4: Chirality transfer in allylic aminations.



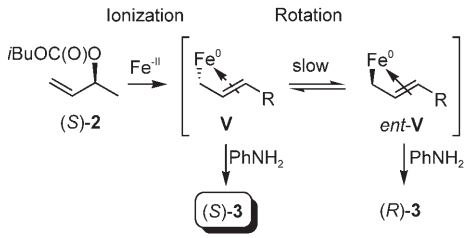
Entry	R	Substrate (*ee* [%][a])	Cond.[b]	Product[c]	*ee* [%][a]	Yield [%][d]
1	Ph	(*S*)-**9**	A	(*S*)-**10**	86	–
2		(94)	B		83	15
3			C		84	62
4	H	(*S*)-**2**	A	(*S*)-**3**	87	–
5		(92)	B		82	36
6			C		80	84

[a] According to HPLC using Chiracel columns. [b] Conditions: A) 1 mmol substrate, 2 mmol aniline, 250 μL DMF, 80 °C, 5 h; B) 1 mmol substrate, 2 mmol aniline, 10 mol % $[Bu_4N][Fe(CO)_3(NO)]$, 10 mol % PPh_3, 250 μL DMF, 80 °C, 5 h; C) 1 mmol substrate, 2 mmol aniline, 5 mol % $[Bu_4N][Fe(CO)_3(NO)]$, 5 mol % PPh_3, 30 mol % Pip·HCl, 250 μL DMF, 80 °C, 5 h. [c] The absolute configuration was assigned by comparison to the literature. [d] Yield of isolated product.

corresponds nicely with the observations made in the allylic alkylation of malonic acid derivatives.[3] Interestingly, only a small decrease in the enantiopurity was observed in the allylic amination of (*S*)-**2** (Table 4, entries 4–6). We were pleased to find that the additive had no influence on the chirality transfer.

This result is remarkable since the chirality of the α-carbon atom in the in situ generated σ-allyl iron complex **V** is conserved only through coordination to the C–C double bond, thus preventing fast rotation around the C–C single bond, which would result in a loss of stereochemical information (Scheme 3). Furthermore, with regard to the observed strong substituent effects, a stereospecific ionization by a S_N2 mechanism appears improbable.

Herein, our results on the first iron-catalyzed allylic amination of allyl carbonates are summarized. As compared to the already established Rh-catalyzed procedure, this protocol is distinguished in particular by the use of the



Scheme 3. Stereoselectivity in allylic aminations.

inexpensive and nontoxic iron catalyst $[Bu_4N][Fe(CO)_3(NO)]$, the simple working procedure, and the high stereo- and regioselectivity, especially in the amination of higher-substituted allyl carbonates.[13]

Various allyl carbonates are converted under the described conditions into essentially regio- and stereoisomerically pure allyl amines. The use of secondary amines as N nucleophiles proved to be problematic as a result of catalyst decomposition. However, this side reaction is retarded in the presence of catalytic amounts of piperidinium chloride as a buffer. The observations and results obtained within the development of the iron-catalyzed allylic amination allowed for important insights into the stability and reactivity of the iron catalysts. Based on these results, future work will concentrate on the development of CO-free iron(−II) complexes, which might possess higher stability toward basic amines.

Experimental Section

General procedure for the allylic amination: In a 2-mL Wheaton vial equipped with a stirring bar and a Mininert valve, a mixture of $[Bu_4N][Fe(CO)_3(NO)]$ (20.6 mg, 0.05 mmol), PPh_3 (13.2 mg, 0.05 mmol), and Pip·HCl (37.1 mg, 0.3 mmol) in DMF (250 μL) under argon was stirred for 15 min at 80 °C. After cooling to ambient temperature, the yellow-brown suspension was stirred further for 15 min before addition of the aniline derivative (2 mmol) and the allyl carbonate (1 mmol). The closed system was heated at 80 °C until full conversion of the carbonate (TLC analysis). Purification was performed directly by column chromatography (SiO_2, isohexane/ethyl acetate) of the cooled reaction mixture. The products were obtained as air- and in some cases light-sensitive, colorless oils.

Received: June 6, 2006
Published online: August 9, 2006

Keywords: allylic amination · arylamines · homogeneous catalysis · iron · regioselectivity

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