Allylic Substitution

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Ligand-Dependent Mechanistic Dichotomy in Iron-Catalyzed Allylic Substitutions: σ-Allyl versus π-Allyl Mechanism**

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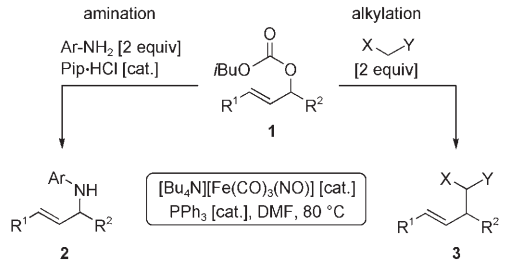
Dedicated to Prof. Wolfgang Kreiser on the occasion of his 70th birthday

Selective C–C bond formation is vitally important in organic chemistry. Transition-metal catalyzed allylic substitution has evolved as a powerful tool in this field.[1] In the presence of enantiopure transition-metal catalysts based on Pd,[2] Mo,[3] Ir,[4] Ru[5], or Ni,[6] enantiomerically enriched products are accessible in good yields starting from racemic material, which is a consequence of the fluctuating character of the intermediate π-allyl metal complexes. In the presence of rhodium[7] or iron catalysts[8] however, a slow isomerization of the σ-allyl metal species initially formed is observed, and in the subsequent nucleophilic substitution, retention of constitution and configuration of the starting material occurs. Hence, both procedures might be regarded as complementary to each other.

The use of an iron catalyst is attractive because of its lower price and low toxicity.[9] Based on preliminary studies by Roustan et al.,[10] and Xu and Zhou,[11] we recently successfully developed a highly regioselective iron-catalyzed allylic alkylation[8a] and amination[8b] (Scheme 1).



Scheme 1. Iron-catalyzed allylic amination and alkylation. Pip = piperidine.

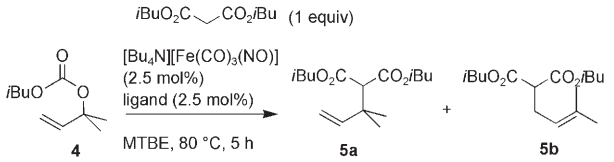
For synthetic application, we wished to improve our procedure for three reasons: a) an excess of pronucleophile is not acceptable from an economic point of view, b) the use of an alternative solvent could pave the way for the allylation of less stabilized nucleophiles, and c) the development of a procedure for the allylic substitution by a π-allyl mechanism is desirable and would allow the use of iron catalysts as an alternative to the existing methods for asymmetric allylic substitutions which use well-established metal complexes.[12]

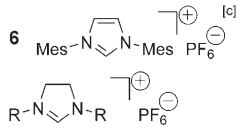
Herein we present a ligand-dependent mechanistic dichotomy in iron-catalyzed allylic substitution, which not only fulfils the requirements mentioned in (a) and (b) above, but also allows the reaction to follow the unprecedented π-allyl iron mechanism (c). The latter aspect represents one of the basic requirements for the development of an asymmetric allylic substitution.

N-Heterocyclic carbenes (NHC ligands) are amongst the most successful ligands in transition-metal catalysis.[13] The σ-donor character of these ligands in combination with the resulting higher nucleophilicity of the coordinated metal ions makes these ligands an attractive choice for iron-catalyzed allylic substitutions (Table 1).[14]

The original procedure could be improved significantly. Unlike DMF, methyl *tert*-butyl ether (MTBE) is more stable toward reactive nucleophiles and therefore was the better solvent. Furthermore, almost complete conversion was

Table 1: NHC ligands for allylic substitutions.



Entry[a]	Ligand[15]		Base[15]	5a/5b[b]	Conv. [%][b]
1	**6**	 [c]	KO*t*Am[d]	10:90	92
2	**7**	R = 2,4,6-$(CH_3)_3C_6H_2$	KO*t*Am[d]	9:91	98
3	**8**	R = 2,6-$(i\text{Pr})_2C_6H_3$		33:67	38
4	**9**	R = 4-$MeOC_6H_4$		63:37	12
5	**10**	R = *i*Pr	$NaNH_2$	84:17	68
6	**11**	R = Ph_2CH		87:13	66
7	**12**	R = *t*Bu		91:9	74

[a] All reactions were performed on a 1-mmol scale in MTBE under an atmosphere of N_2. [b] Determined by GC. [c] Mes = 2,4,6-trimethylphenyl. [d] KO*t*Am = potassium 2-methylbutan-2-olate.

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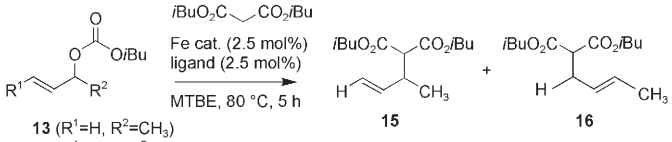
observed using stoichiometric amounts of each reactant (Entry 2, Table 1). Surprisingly, an inversion of the regioselectivity when compared to the original reaction was observed, leading to predominant formation of product **5b** (Entry 2, Table 1). Steric reasons seem to be responsible for this unexpected result. Thus the use of a sterically more hindered *i*Pr-group in the *o*,*o*′-position of the aryl substituent leads to a significant shift of regioselectivity toward the *ipso* substitution product **5a** (Entry 3, Table 1). A further increase in the size of the substituent at nitrogen was achieved by the introduction of sp^3-hybridized carbon atoms. The increased steric demand causes the predominant formation of product **5a** (Entries 5–7, Table 1). Use of the *tert*-butyl group in ligand **12** led to product **5a** in high selectivity (Entry 7, Table 1).[16]

The varying regioselectivity suggests a reaction path that differs from the σ-allyl mechanism. An alternative is the unprecedented catalytic reaction with a π-allyl iron complex.[17] As the constitution of the allyl carbonate should only have a minor influence on the product distribution in this case, the two regioisomeric carbonates **13** and **14** were transformed into the products **15**/**16** in the presence of ligand **7** and **12**. The use of **7** leads to the formation of an identical mixture of regioisomers **15** and **16** (Entries 1 and 2, Table 2) and is comparable to the product distribution obtained in the presence of $[Pd(PPh_3)_4]$ under identical conditions. In the presence of ligand **12** however, it is the position of the leaving group in **13**/**14** which directs the regioselective course of the reaction (Entries 3 and 4, Table 2).

Table 2: Influence of the ligand on regioselectivity.

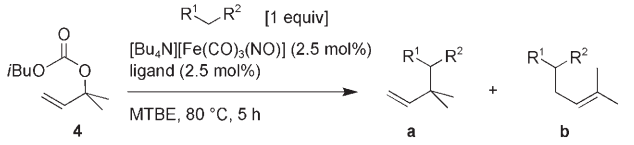


Entry[a]	Carbonate	Ligand	**15**/**16**[b]	Yield [%][b]
1	**13**	**7**	17:83	67 (72)
2	**14**		15:85	63 (68)
3	**13**	**12**	91:9	71 (78)
4	**14**		12:88	64 (66)

[a] All reactions were performed on a 1-mmol scale in MTBE under an atmosphere of N_2. [b] Yield of isolated product; yield determined by GC in brackets.

The σ–π–σ isomerization in the presence of ligand **7** might be the consequence of a slow attack of the nucleophile at the allyl iron intermediate. Hence, more reactive nucleophiles should influence the regioselective course of the reaction. To test this hypothesis, various malonic acid derivatives, differing in nucleophilicity and acidity, were allylated (Table 3). The allylation is broadly applicable in the presence of ligand **7** or **12**. In each case the reaction proceeded with almost full conversion. However, depending on the ligand and the pK_a value, significant shifts in the regioselectivity were observed. Whereas the presence of the sterically hindered ligand **12** results in the predominant formation of the *ipso* substitution product (Entries 2, 4, 6, 8, 10, Table 3), the regioselective course of the reaction in the presence of ligand **7** is directed mostly by the acidity and nucleophilicity of the carbanion generated in situ. Hence, the fast deprotonation of malodinitrile and the high nucleophilicity of the anion formed (*s* 0.67, *N* 19.36)[19] leads to a fast substitution of the allyl iron complex. It appears that the σ–π–σ isomerization is not fast enough under these conditions, and consequently the formation of the *ipso* substitution product **20a** is favored (Entry 9, Table 3).[20]

Table 3: Influence of the nucleophile on regioselectivity.

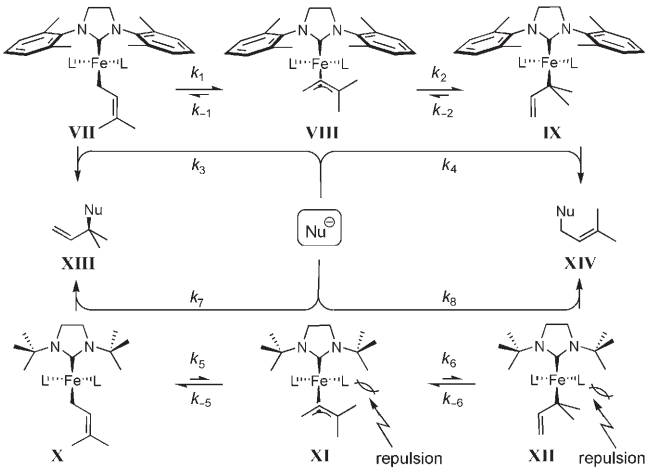


Entry[a]	Ligand	R^1	R^2	pK_a[b]	Product	**a**/**b**[c]	Yield [%][c]
1	**7**	CO_2iBu	CO_2iBu	16.4	**5**	9:91	79
2	**12**					91:9	84
3	**7**	CO_2iBu	$C(O)CH_3$	14.2	**17**	15:85	76
4	**12**					94:6	74
5	**7**	CO_2iBu	CN	13.1	**18**	74:26	85
6	**12**					95:5	88
7	**7**	SO_2Ph	CN	12.0	**19**	60:40	86
8	**12**					80:20	87
9	**7**	CN	CN	11.1	**20**	80:20	76
10	**12**					99:1	85

[a] All reactions were performed on a 1-mmol scale in MTBE under an atmosphere of N_2. [b] Entries 1–6 refer to the corresponding ethyl esters.[18] [c] Yield of isolated product.

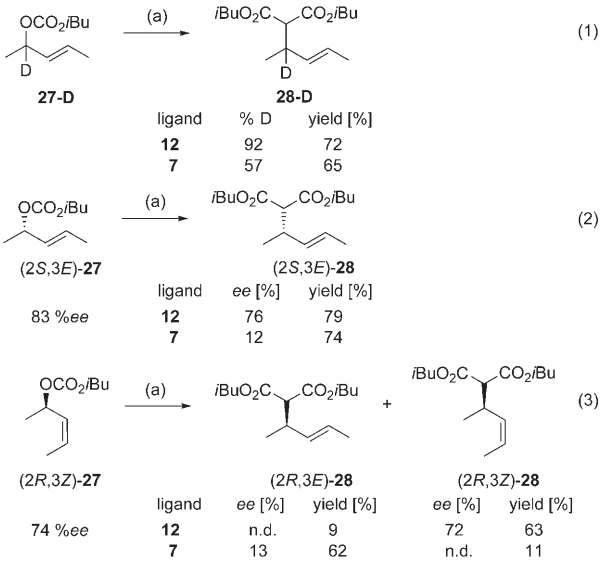
The results obtained so far are summarized in the mechanistic model in Scheme 2. Assuming that in the presence of ligand **7** or **12**, a σ-allyl iron species such as **VII**/**X** is formed, two subsequent reactions are possible. Species **VII** and **X** could be transformed into the desired product **XIII** in a fast substitution reaction, or, if this reaction is slower and the ligand-created steric environment tolerates a fluctuation of the metal in the allyl terminus, the formation of the more easily substituted σ-allyl iron complex **IX** from **VII** is possible. A planar aryl substituent in **7** could facilitate such a fluctuation, whereas a *tert*-butyl group as in **12** generates unfavorable steric interactions and thus disfavors the formation of π-allyl complex **XI** from **X** (Scheme 2).

The optimized reaction conditions have a great impact on the reaction scope. The use of MTBE as an inert solvent enables the use of preformed nucleophiles in the reaction.[21] The possibilities connected with this important result are exemplified in the reaction of azlactone **21** (Scheme 3). Whereas under salt-free conditions almost no reaction was observed, after deprotonation of **21**, the reaction to form allylation product **23** was successful, and furthermore the

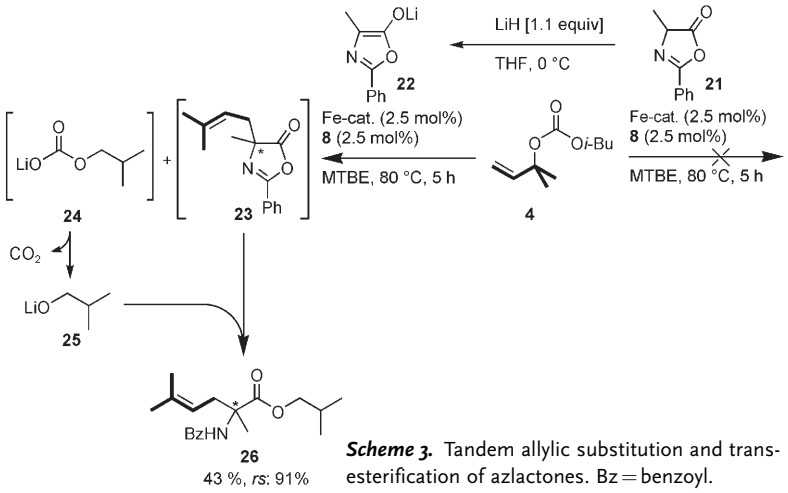


Scheme 2. Mechanistic model for the ligand-dependent dichotomy.

isobutoxide **25** generated in situ reacted with **25** in a subsequent transesterification/ring opening sequence to yield isobutyl ester **26**.



Scheme 4. Ligand influence in allylic substitutions of **27**. Reagents and conditions: a) $[Bu_4N][Fe(CO)_3(NO)]$ (2.5 mol%), ligand (2.5 mol%), MTBE, 80°C. n.d. = not determined.



Scheme 3. Tandem allylic substitution and transesterification of azlactones. Bz = benzoyl.

The consequences of the mechanistic dichotomy on stereo- and regioselectivity in allylic substitutions of 1,2-disubstituted isomeric carbonates such as **27** were investigated (Scheme 4). The allylic substition of deuterated carbonate **27-D** occurred only in the presence of ligand **12** selectively at the deuterated carbon atom [Eq. (1), Scheme 4]. Use of the enantiomerically enriched carbonates (*E*)- and (*Z*)-**27** using ligand **12** resulted in only a small decrease in enantioselectivity. The substitution products **28** were formed with formal retention of the configuration and the geometry at the double bond stayed intact.[22] In contrast, the same reactions in the presence of aryl-substituted ligand **7** led to a loss of constitutional and configurational information of the carbonates **27** [Eq. (2) and (3), Scheme 4].

We have presented a ligand-dependent mechanistic dichotomy in iron-catalyzed allylic substitutions. The use of *tert*-butyl-substituted NHC ligand **12** led to the development of a significantly improved procedure which features the use of exact stoichiometric amounts of the pronucleophile and a solvent change from DMF to MTBE. The latter aspect is of great importance, as it allows the allylation of non-stabilized or reactive nucleophiles. Furthermore, we were able to show that in the presence of ligand **12**, both regio- and stereoconservative allylic substitution is possible in which the double bond geometry stays intact. The use of aryl-substituted ligand **7** allowed for the first time allylation by the π-allyl mechanism, which is complementary to that with **12**. The loss of constitutional information of the starting material should, in the case of a fast σ–π–σ-isomerization, set the stage for the successful development of a iron-catalyzed, asymmetric, dynamic–kinetic allylic substitution.

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