Iridium-Catalyzed Enantioselective Allylic Substitutions with Aliphatic Nitro Compounds as Prenucleophiles

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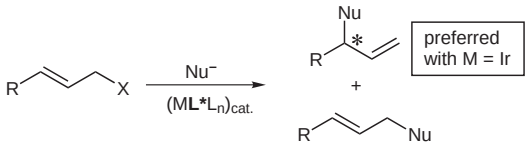
Dedicated to Professor Dieter Enders on the occasion of his 60th birthday.

Abstract: Enantioselective Ir-catalyzed allylic alkylations with nitroalkanes and ethyl nitroacetate as nucleophiles are reported. Up to 99% ee was achieved using catalysts prepared by in situ activation of mixtures of phosphorus amidites and $[Ir(COD)Cl]_2$. The method was applied to a synthesis of the antidepressant (1*S*,2*R*)-*trans*-2-phenylcyclopentanamine.

Key words: allylic substitution, iridium, catalysis, nitroalkanes, ring-closing metathesis

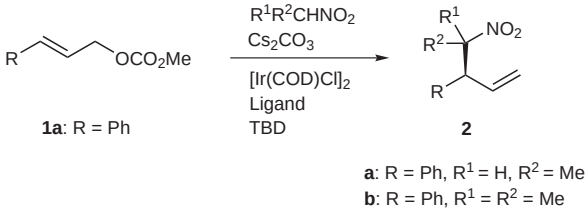
The transition-metal-catalyzed asymmetric allylic substitution is an established method for the generation of stereogenic centers.[1] Recently, the traditional palladium catalysis has been supplemented by iridium catalysis.[2] With Ir catalysts the nucleophilic displacement according to Scheme 1 leads preferentially to the branched, chiral substitution product, while Pd catalysts favor the linear achiral product. Over the last few years, excellent results with respect to regio- as well as enantioselectivity have been achieved for Ir-catalyzed substitutions with C-,[3] N-,[4,5] and O-nucleophiles.[6] As C-nucleophiles, mainly malonates have so far been used. We have now successfully probed nitronates and a new variant of the versatile combination of the allylic substitution with ring-closing metathesis (RCM).



Scheme 1

Aliphatic nitro compounds are valuable intermediates in organic synthesis due to the diversity of their chemistry.[7] In asymmetric synthesis, nitro aldol additions and Michael reactions have mainly been studied. The Ir-catalyzed allylic substitutions according to Scheme 2 open an access to chiral nitroalkenes of the type **2**, which are not directly accessible otherwise.

So far the best catalysts for the Ir-catalyzed allylic substitution have been obtained by combining $[Ir(COD)Cl]_2$ with phosphorus amidites **L1** or **L2** (Figure 1).[8] These undergo CH activation upon treatment with base, TBD {1,5,7-triazabicyclo-[4.4.0]dec-5-ene} in this work, thus generating a P,C-chelate complex of high activity.[4a,5]



Scheme 2

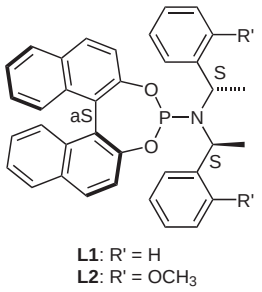


Figure 1

Application of the above protocol to the reaction between cinnamyl methyl carbonate (**1a**) and a primary as well as secondary nitro compound (Scheme 2, Table 1 and General Procedure) furnished branched products **2** in good yields and with excellent regio- and enantioselectivity. Only the reaction with nitromethane gave poor results. Despite extensive screening of reaction conditions, complex mixtures were obtained, which contained mono- and bis-allylation product along with various unidentified compounds.

Primary nitro compounds are important intermediates, which can be transformed, for example, into aldehydes[10] or nitriles.[11] Therefore, the reaction with ethyl nitroacetate, a synthesis equivalent of nitromethane, was investigated (Scheme 3, Table 2). With this compound the reaction proceeded fast without an additional base.

Saponification of the ester **3a** with NaOH, prior to intended thermal decarboxylation, caused shift of the double bond into conjugation with the phenyl group. Krapcho deethoxycarbonylation experiments using standard

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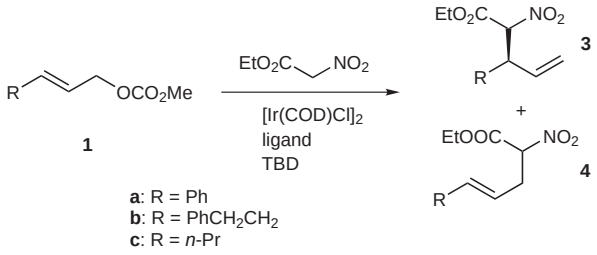
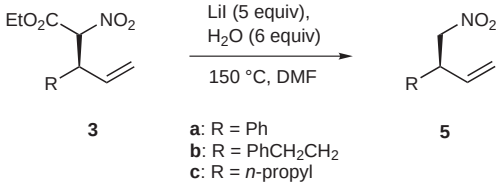
Table 1 Allylic Substitutions (Scheme 2)[9]

Entry	Ligand	R^1	R^2	Time (h)[a]	Ratio[b]	Yield (%)[c]	ee (%)[d]
1	**L2**	H	H	>48	[e]		
2	**L1**	H	Me	<16	99:1	71[f]	95, 85
3	**L2**	H	Me	<16	99:1	85[f]	98, 96
4	**L2**	Me	Me	<16	96:4	84	99

[a] Reaction time.
[b] Ratio of branched/linear products.
[c] Yield of isolated products.
[d] Determined by HPLC; column: Daicel Chiralcel AD-H, 250 × 4.6 mm, 5 μm, and guard cartridge 10 × 4 mm, 5 μm; eluent: *n*-hexane–*i*-PrOH, 99:1, flow: 0.5 mL/min; t_R [(+)-**2a**] = 13.9 min (major), t_R [(–)-**2a**] = 14.5 min, t_R [(–)-*epi*-**2a**] = 14.6 min, t_R [(+)-*epi*-**2a**] = 16.3 min (major), t_R[(–)-**2b**] = 12.3 min, t_R[(+)-**2b**] = 13.1 min (major).
[e] Nonselective reaction, cf. text.
[f] 1:1 Mixture of epimers (relative configuration not determined), that were separated by column chromatography and analyzed individually.



Scheme 3



Scheme 4

conditions[12] did not give satisfactory results either. After some experimentation we found modified conditions (LiI, H_2O, DMF) providing the desired primary nitro compounds **5** in good to excellent yields (Scheme 4, Table 3, General Procedure).

In previous work, the combination of the Ir-catalyzed allylic substitution and RCM has been established as powerful method for the synthesis of biologically active compounds.[14] Here we used this strategy for a synthesis of (1*S*,2*R*)-*trans*-2-phenylcyclopentanamine (**9**, Scheme 5), a compound that itself shows antidepressant activity,[15] and its *N*-isopropylsulfonyl derivative, which displays high activity as an AMPA potentiator.[16] The securely established absolute configurations of these compounds corroborate the assignments given in Scheme 3 and Table 2.

The synthesis of (1*S*,2*R*)-**9** is described in Scheme 5. The first step is an Ir-catalyzed reaction of **1a** with 4-nitro-1-butene, which was carried out with *ent*-**L2** as ligand

Table 2 Allylic Substitutions (Scheme 3)

Entry	Substrate	Ligand	Time (h)	**3**/**4**	Yield (%)	ee[a] (%)
1	**1a**	**L1**	5	99:1	85	96[b]
2	**1a**	**L2**	0.5	99:1	90	98[b]
3	**1b**	**L1**	5	63:37	95	96[c]
4	**1b**	**L2**	3	78:22	86	98[c]
5	**1c**	**L1**	4	77:23	97	95[d]
6	**1c**	**L2**	0.5	90:10	92	99[d]

[a] Determined for compounds **5**, which were prepared according to Scheme 4.
[b] Determined by HPLC; column: Daicel Chiralcel OD-H, 250 × 4.6 mm, 5 μm, and guard cartridge 10 × 4 mm, 5 μm; eluent: *n*-hexane–*i*-PrOH, 90:10, flow: 0.5 mL/min; t_R [(–)-**5a**] = 20.4 min, t_R [(+)-**5a**] = 31.2 min (major).
[c] Determined by HPLC; column: Daicel Chiralcel OJ-H, 250 × 4.6 mm, 5 μm, and guard cartridge 10 × 4 mm, 5 μm; eluent: *n*-hexane–*i*-PrOH, 90:10; flow: 0.5 mL/min; t_R [(–)-**5b**] = 25.7 min (major); t_R [(+)-**5b**] = 27.9 min.
[d] Determined by GC; column: Chrompack permethyl β-cyclodextrin, Cp-Cyclodextrin-B-236-M-19 (25 m × 0.25 mm), 60 °C for 120 min, then gradient 1 °C/min; injection temp: 200 °C; t_R [(–)-**5c**] = 133 min, t_R [(+)-**5c**] = 135 min (major).

Table 3 Modified Krapcho Deethoxycarbonylation (Scheme 4)[13]

Entry	Substrate	Product	Yield (%)
1	**3a**	**5a**	70
2	**3b**	**5b**	75
3	**3c**	**5c**	95

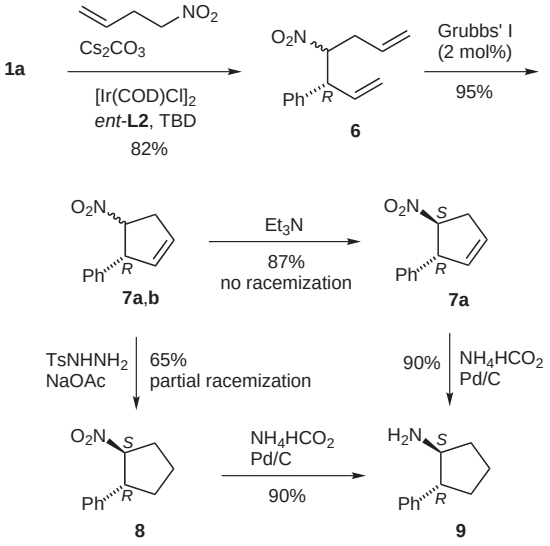
according to the General Procedure. The substitution product **6** was obtained as mixture of epimers with excellent regio- and enantioselectivity of 93%.[17] The linear byproduct was not found. Another route to **6** was Pd-catalyzed allylation of **5a** with allyl methyl carbonate (65% yield).

Transformation of **6** into **7a**,**b** by RCM was effected by heating a solution of **6** and Grubbs' I catalyst (2 mol%) in CH_2Cl_2 at reflux for five hours. The epimeric cyclopentenes **7a** and **7b** were separated by column chromatography and their relative configurations were determined by measurement of NOE between 1-H and 5-H: 0.4% for the *trans*-isomer (**7a**) and 4.9% for the *cis*-isomer (**7b**).

Further steps required were epimerization of **7a**,**b** to get the pure *trans*-isomer **7a** and reduction of the nitro group and the C–C double bond. If the latter step is carried out by transition-metal-catalyzed hydrogenation, it is usually accompanied by epimerization in an allylic position.[18] We have shown that this problem can be overcome by use of diimide as reducing agent.[14a] Hence, a solution of **7a**,**b**, $TsNHNH_2$ (50 equiv) and NaOAc (100 equiv) in dimethoxyethane–water was heated at reflux. We were delighted that pure **8** was formed as product in 65% yield, i.e., hydrogenation as well as epimerization had occurred. However, the enantiomeric excess of **8** was only 84%, i.e. racemization, probably via the intermediary nitronate,[19] was a competing third reaction.

As a consequence, the epimerization and the hydrogenation step were carried out separately. Thus, epimerization of **7a**,**b** by treatment with triethylamine in DMSO–water according to a method of Kingsbury[19] furnished a 10:1 mixture of *trans*- and *cis*-**7**. The ee was not altered under these conditions. Column chromatography gave pure **7a** in 80% and **7b** in 8% yield. The latter was subjected once more to the epimerization conditions, giving a further 7% yield of **7a**, i.e. a total yield of 87% of diastereomerically pure *trans*-**7** was obtained.

Reduction of **7a** with ammonium formate in methanol, using Pd/C as catalyst,[20] furnished the amine **9** in 90% yield.[21] The enantiomeric excess of both **7a** and **9** was 93%. Furthermore, the latter contained less than 4% of the *cis*-isomer (^{1}H NMR).



Scheme 5

Acknowledgment

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(9) **General Procedure for Allylic Alkylation**
Under argon at r.t., a solution of $[Ir(COD)Cl]_2$ (0.02 mmol) and **L*** (0.04 mmol) in dry THF (1.0 mL) was treated with TBD (0.08 mmol). After stirring for 2 h at r.t. the allylic carbonate (1.0 mmol) was added, and the mixture was stirred for 5 min at r.t. Then the nitro compound (1.5 mmol) and eventually Cs_2CO_3 (1.0 mmol) were added and the mixture was stirred until GCMS indicated complete conversion. The mixture was partitioned between H_2O and EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was analyzed with respect to the content of branched and linear product by ^1H NMR. The pure reaction products were obtained by flash chromatography and kugelrohr distillation.
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(13) **General Procedure for the Preparation of Primary Nitro Compounds 5 from Esters 3 (Scheme 4)**
Under argon, a solution of ester **3**, LiI (5 equiv), H_2O (6 equiv) and a trace of di-*tert*-butyl-1,4-hydroquinone in DMF was heated at 150 °C over a period of 5 h. Then, sat. NaCl solution was added and the mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo, and the residue was subjected to flash chromatography.
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(17) Both enantiomers of **6** were prepared. The ee was obtained after transformation to **7a**. The ee of the latter was determined by HPLC; column: Daicel Chiralcel OJ-H, 250 × 4.6 mm, 5 μm, and guard cartridge 10 × 4 mm, 5 μm; eluent: *n*-hexane–*i*-PrOH, 90:10; flow: 0.5 mL/min; t_R [(–)-**7a**] = 23.5 min, t_R [(+)-**7a**] = 29.9 min (major).
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(21) (a) The absolute configuration of **9** was assigned by comparison of HPLC data of the *N*-isopropylsulfonyl derivative of **9** with reported data (ref. 16) and on the basis of the optical rotation of (1*S*,2*R*)-**9**·HCl (93%ee): $[\alpha]_D^{20}$ +56.6; reported: $[\alpha]_D^{23}$ +68.8 (99% ee), see ref. 21b. The ee of **9** was determined by HPLC; column: Daicel Chiracel OD-H, 250 × 4.6 mm, 5 μm, and guard cartridge 10 × 4 mm, 5 μm; eluent: *n*-hexane–*i*-PrOH, 99:1; flow: 0.5 mL/min; t_R [(1*S*,2*R*)-**9**] = 36.9 min, t_R [(1*R*,2*S*)-**9**] = 40.6 min.
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