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Asymmetric aminocarbonylation of iodoalkenes in the presence of α-phenylethylamine as an *N*-nucleophile

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ABSTRACT

Iodoalkenes, such as 2-iodo-bornene, 17-iodoandrost-16-ene, 3-methoxy-17-iodoestra-1,3,5(10),16-ene, 3β-hydroxy-20-iodopregna-5,20-diene and 3β-hydroxy-12-iodo-5α,25*R*-spirost-11-ene were aminocarbonylated with enantiomerically pure and racemic α-phenylethylamine as the *N*-nucleophile in the presence of palladium(0) catalysts. Monodentate and bidentate (chiral and achiral) phosphines were used as ligands in the catalytic system. All diastereoisomers of the corresponding carboxamides were characterised as pure stereoisomers using both α-phenylethylamine and iodoalkene in enantiomerically pure form. The diastereoisomers were obtained in moderate to high yields in a chemoselective reaction, *i.e.*, carboxamides due to single carbon monoxide insertion were formed exclusively, with no double CO insertion leading to 2-ketocarboxamides. Diastereoselectivities of the aminocarbonylation were investigated using the *N*-nucleophile in racemic form by the systematic variation of the catalyst.

1. Introduction

The palladium-catalysed aminocarbonylation of aryl and alkenyl halides (especially iodides and bromides),[1] as well as their triflate synthetic surrogates, is one of the most widely used catalytic reactions. The facile introduction of carboxamide and 2-ketocarboxamide functionalities into model compounds and skeletons of practical importance has made this reaction very popular in synthesis and has been summarised in treatises[2] and reviews.[3] The industrial importance of these carbonylations has also been reported.[4]

Among the great variety of substrates, terpenoic iodoalkenes such as iodobornene and iodocamphene, have been functionalised in palladium-catalysed aminocarbonylations using various primary and secondary amines including amino acid methyl esters.[5] As for the homogeneous catalytic functionalization of a related steroidal skeleton,[6] the introduction of carboxamide functionality into androstane,[7] estrane[8] and spirostane[9] backbones via palladium-catalysed aminocarbonylation is one of the most powerful methodologies for the synthesis of steroidal carboxamides of pharmaceutical importance.

Recently, the diastereoselective aminocarbonylation of steroid[10] and camphene[11] substrates possessing an iodoalkenyl functionality was carried out in the presence of 2,2′-diamino-1,1′-binaphthalene (BINAM) as an *N*-nucleophile possessing an axial element of chirality.

Herein, a systematic study on the diastereoselective aminocarbonylation of chiral iodoalkenes with one of the most widely used chiral amines, α-phenylethylamine is described. This work was inspired by the sporadic results on asymmetric (diastereoselective) aminocarbonylation and the lack of structure–reactivity relationships, as well as by the potential importance of the target steroidal compounds with carboxamide functionality.

2. Results and discussion

2.1. Aminocarbonylation of 2-iodobornene 1 with α-phenylethylamine (PEA)

2-Iodobornene **1** was used as substrate in racemic and enantiomerically pure (1*R*,4*R*)-**1** or (1*S*,4*S*)-**1** form in aminocarbonylation with α-phenylethylamine as the *N*-nucleophile (Scheme 1). Highly active coordinatively unsaturated palladium(0) catalysts,[12] formed in situ by the reaction of palladium(II) acetate and two molar equivalents of monophosphine (PPh_3 or $P(tBu)_3$) or an equimolar amount of diphosphine, such as (*S*,*S*)-BDPP, (*R*)-BINAP and (*S*,*S*)-CHIRAPHOS, were used. The aminocarbonylation of **1** can be considered perfectly chemoselective resulting in the

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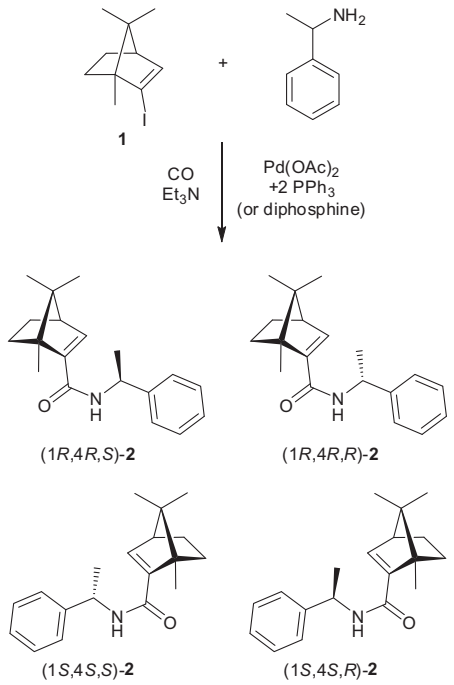

Scheme 1. Aminocarbonylation of 2-iodobornene (**1**) with α-phenylethylamine (all carboxamide stereoisomers are indicated).

formation of the corresponding carboxamide **2**. Considering the detection limit of NMR methods, it can be stated that double carbon monoxide insertion leading to 2-ketocarboxamides could only occur in less than 2%.

As a first step, α-phenylethylamine was used as the *N*-nucleophile in enantiomerically pure (*S*)-PEA form, while **1** was used both as an enantiomerically pure and racemic substrate. In order to identify the epimers of **2**, both (1*R*,4*R*,*S*)-**2** and (1*S*,4*S*,*S*)-**2** were synthesised using the stereochemically pure iodoalkene enantiomers, (1*R*,4*R*)-**1** and (1*S*,4*S*)-**1**, respectively (Table 1, *entries 11, 12*).

The epimeric composition of the reaction mixture carried out with racemic iodoalkene was determined quantitatively by ^{1}H NMR. The carboxamide product mixture was obtained upon evaporation of the solvent and was used for NMR analysis. For this purpose, the perfectly separated signals of the olefinic region of the ^{1}H NMR was used (Fig. 1).

The following conclusions regarding the diastereoselectivities of the reaction influenced by the catalyst can be drawn; as expected, the two epimers are formed in practically a 1:1 ratio when the racemic iodoalkene and the enantiomerically pure *N*-nucleophile was used in equimolar amount and essentially complete conversions were achieved (*entries 1–4*). When the conversion was kept at lower values, negligible diastereoselection was observed (*entry 5*). Low diastereoselectivities were obtained when racemic iodoalkene **1** was used in twofold excess relative to the amine. Both the application of the achiral phosphine ligands (*entries 6, 7*) and that of the chiral bidentate ligands (*entries 8–10*) yielded low diastereoselectivities. The CHIRAPHOS-containing system, which is able to form five-membered chelate palladium-complexes, showed the lowest catalytic activity. It was proved unequivocally that no racemization took place either at the stereogenic centres of iodoalkene and amine under aminocarbonylation conditions. Using both (*S*)-PEA and iodoalkene **1** in enantiomerically pure form [(1*R*,4*R*) or (1*S*,4*S*)], the corresponding single enantiopure epimers were synthesised (*entries 11 and 12*).

In the 'opposite' case, *i.e.* using enantiomerically pure iodoalkene and racemic chiral amine, similarly low diastereoselectivities were obtained. The aminocarbonylation of (1*R*,4*R*)-2-iodobornene **3** with racemic chiral amine PEA resulted in close to 1:1 mixtures (Table 2). As above, no racemization of the enantiomerically pure iodoalkene (1*R*,4*R*)-**1** was observed under the reaction conditions Using enantiomerically pure (1*R*,4*R*)-**1** (or (1*S*,4*S*)-**1** and (*R*)-PEA the corresponding single epimers were synthesised (*entries 6 and 7*).

2.2. Aminocarbonylation of steroidal iodoalkenes 3, 5, 7 and 9 with α-phenylethylamine

Chiral steroidal substrates (17-iodoandrost-16-ene **3**, 3-methoxy-17-iodoestra-1,3,5(10),16-ene **5**, 3β-hydroxy-20-iodopregna-5,20-diene **7** and 3β-hydroxy-12-iodo-5α,25*R*-spirost-11-ene **9** (Scheme 2)) possess 'natural' configurations at the key positions, for instance, at C-5, C-8, C-9, C-10, C-13 and C-14 in case of the androstane skeleton, were aminocarbonylated with PEA under standard aminocarbonylation conditions.

In general, the use of various steroids as enantiomerically pure substrates resulted in the formation of a nearly 1/1 epimeric composition of the products when racemic PEA was used as the nucleophile (Table 3). It is noteworthy that the aminocarbonylation is highly selective toward carboxamide formation. No 2-ketocarboxamide

Table 1
Aminocarbonylation of 2-iodobornene **1** with (*S*)-PEA in the presence of in situ Pd-(chiral) phosphine catalysts[a]

Entry	**1**		PEA		PR_3	Epimeric composition of **2**[b] (1*R*,4*R*,*S*)-**2**/(1*S*,4*S*,*S*)-**2**
	abs. conf.	mmol	abs. conf.	mmol		
1	Racemic	0.5	(*S*)	0.5	PPh_3	49/51
2	Racemic	0.5	(*S*)	0.5	P(*t*Bu)$_3$[c]	50/50
3	Racemic	0.5	(*S*)	0.5	(*R*)-BINAP	50/50[d]
4	Racemic	0.5	(*S*)	0.5	(*S*,*S*)-BDPP	50/50
5	Racemic	0.5	(*S*)	0.5	(*S*,*S*)-CHIRAPHOS	48/52[e]
6	Racemic	1	(*S*)	0.5	PPh_3	51/49
7	Racemic	1	(*S*)	0.5	P(*t*Bu)$_3$[c]	52/48
8	Racemic	1	(*S*)	0.5	(*R*)-BINAP	52/48
9	Racemic	1	(*S*)	0.5	(*S*,*S*)-BDPP	50/50
10	Racemic	1	(*S*)	0.5	(*S*,*S*)-CHIRAPHOS	50/50
11	(1*R*,4*R*)	0.5	(*S*)	0.5	PPh_3	100/0
12	(1*S*,4*S*)	0.5	(*S*)	0.5	PPh_3	0/100

[a] Reaction conditions (unless otherwise stated): 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of tertiary phosphine (or 0.025 mmol of diphosphine); 0.5 mL of triethylamine; solvent: 10 mL DMF; reaction temperature: 50 °C; 1 bar CO, reaction time: 1 h; conversion >98% (based on **1**).
[b] Determined by ^{1}H NMR.
[c] P(*t*Bu)$_3$ HBF_4 was used.
[d] Conversion: 94%.
[e] Conversion: 62%.