Catalysis

Synthesis of Axially Chiral Carboxamides via Aminocarbonylation of Aryl and Vinyl Iodides with 2,2′-Diamino-1,1′-binaphthalene in the Presence of Palladium Catalysts

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Palladium-catalysed aminocarbonylation of iodobenzene and 1-iodocyclohexene with both enantiomerically pure and racemic 2,2′-diamino-1,1′-binaphthalene (BINAM) as *N*-nucleophile was carried out. The mono- and dicarboxamide enantiomers possessing axial chirality were synthesised using (S_{ax})-BINAM. In the possession of these reference compounds the partial chiral kinetic resolution of racemic BINAM was carried out using various optically active bidentate ligands such as (*2S,4S*)-BDPP, (*2S,3S*)-CHIRAPHOS and (*R*)-BINAP. It was revealed by chiral HPLC measurements that up to 10% enantiomeric excess of carboxamides can be achieved in this way. Although with low enantioselection, enantioselectve aminocarbonylation was carried out for the first time.

Introduction

Although a great variety of synthetic methods is available for the synthesis of carboxamides, and is discussed in details in handbooks, treatises, and even textbooks, the transition metal catalysed carbonylation reactions are among the most important ones. In particular, palladium-catalysed aminocarbonylation,[1] enabling the direct synthesis of carboxamides from easily available substrates, provided a real breakthrough in the synthesis of otherwise hardly available carboxamides. Using this methodology, aryl and alkenyl halides (especially iodides and bromides) or the corresponding triflates, their synthetic surrogates, can easily be transformed to carboxamides.[2,3] Some aminocarbonylations of industrial importance were also published.[4]

Both iodoalkenes and *N*-nucleophiles possessing central element of chirality were used in aminocarbonylation, however, sporadic results on the same reaction involving reactants with axial chirality were published. Aminocarbonylation of optically active iodoalkene model compounds such as iodomonoterpenes and iodoandrostenes was carried out in the presence of 2,2′-diamino-1,1′-binaphthalene (BINAM) as nucleophile providing diastereoisomeric hybride compounds containing both axial and central elements of chirality.[5] It is worth noting that binaphthalene derivatives possessing axial element of chirality were used in other homogeneous catalytic reactions such as the palladium-catalysed reaction of 1,1′-binaphthalene-2,2′-ditriflate with chiral and achiral dimethylaluminum derivatives.[6]

In the light of the above findings, it is surprising that no example for the asymmetric aminocarbonylation was published. In this study, encouraged by the importance of enantiomerically pure/enantiomerically enriched compounds containing the axial element of chirality, we decided to carry out the synthesis of enantiomerically pure BINAM-based carboxamides. Additionally, to the best of our knowledge, for the first time, the kinetic resolution of BINAM in aminocarbonylation reaction in the presence of palladium-chiral diphosphine systems was investigated.

Results and Discussion

Aminocarbonylation of iodobenzene (1) and 1-iodocyclohexene (2) with enantiomerically pure chiral diamine, (S_{ax})-BINAM

The aminocarbonylation of iodobenzene (**1**) was carried out in the presence of (S_{ax})-BINAM in order to synthesise the enantiomers of carboxamides as reference compounds for further catalytic investigations (Scheme 1, *upper reaction*). Both dicarboxamide (S_{ax})-**3** and monocarboxamide (S_{ax})-**4** were formed and isolated as chemically pure compounds (*See Experimental, Characterization of the compounds*). An overall conversion of higher than 98% was obtained (ratio of (S_{ax})-**3**/(S_{ax})-**4** was 45/55).

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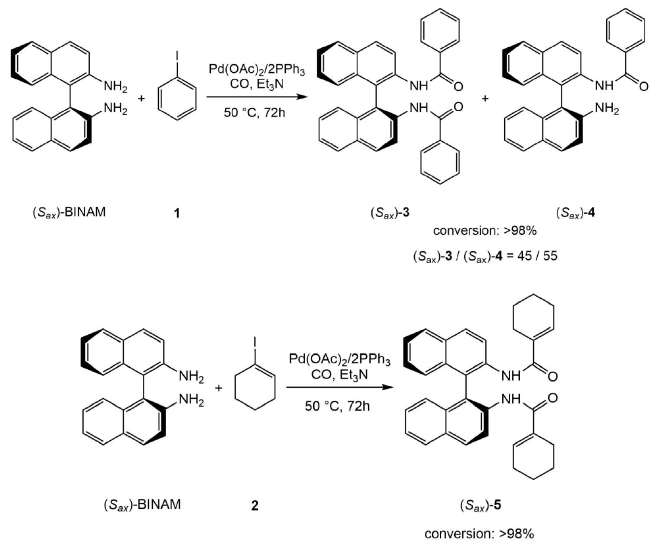


Scheme 1. Aminocarbonylation of iodobenzene (**1**) and 1-iodo-cyclohexene (**2**) in the presence of (S_{ax})-BINAM as *N*-nucleophile.

No double carbon monoxide insertion resulting in 2-ketocarboxamide functionality/functionalities was observed. (It has to be noted that double CO insertion is a common feature using primary and secondary amines as nucleophiles but usually it is a trace reaction in case of aromatic amines like substituted aniline derivatives.[3] The lack of this reaction, *i.e.*, the highly chemoselective reaction towards carboxamides via single carbon monoxide insertion, can be rationalised on the basis of the unfavourable formation of palladium(II)-carbamoyl-acyl intermediate which is a key complex for reductive elimination providing 2-ketocarboxamides.)

It has to be noted that no conversion with bromobenzene was obtained, the corresponding carboxamides were not formed even in traces.

The similar reaction with 1-iodocyclohexene (**2**) substrate was carried out (Scheme 1, *bottom reaction*). The highly reactive iodoalkene provided the corresponding dicarboxamide (S_{ax})-**5**) as a single product. The iodoalkene was practically fully converted. As expected, based on the detailed investigations with iodoalkenes of different structure,[7] no double CO insertion was observed and their presence could not be detected even in traces.

As indicated in Scheme 1, an *in situ* catalytic system formed from $Pd(OAc)_2$ precursor and triphenylphosphine (or in further experiments, enantiomerically pure diphosphines, see below) was used. In this way, highly active, coordinatively unsaturated palladium(0) catalysts can be obtained. The formation of the palladium(0) 'in situ' catalysts, by acting one of the two phosphines as reducing agent while it is oxidized to the corresponding phosphine oxide, was already investigated in details.[8]

As a comparision, a Pd/C catalyst was also tested, *i.e.*, the palladium(II) acetate was replaced, and the reaction was carried out with iodobenzene substrate (**1**) under the same conditions. The substrate was practically fully converted, however, a nearly equimolar mixture of **3**/**4** (49/51) was obtained.

Aminocarbonylation of iodobenzene (1) in the presence of (R_{ax}/S_{ax})-BINAM (racemic) as N-nucleophile

In the next step, the above reaction using racemic BINAM was investigated under chiral conditions, *i.e.*, the application of chiral palladium catalyst was tested. In order to achieve kinetic resolution the palladium(II) acetate-based *in situ* catalyst system containing (*2S,3S*)-CHIRAPHOS, (*2S,4S*)-BDPP and (*R*)-BINAP (Figure 1) was used. These bidentate ligands form 5-, 6- and 7-membered chelate rings, respectively, upon coordination to Pd. As a starting experiment, the PPh_3-containing system was also tested (Scheme 2).

As depicted in Scheme 2, the formation of (S_{ax})-**3**, (R_{ax})-**3**, (S_{ax})-**4** and (R_{ax})-**4** is expected. The enantiomeric composition of the reaction mixtures were determined by chiral HPLC. Perfect baseline separation was achieved with **3** but overlapping peaks of the monocarboxamide enantiomers (S_{ax})-**4** and (R_{ax})-**4** were obtained (See Supporting Information).

The aminocarbonylation reactions carried out under atmospheric carbon monoxide pressure resulted in the formation of both di- (**3**) and monocarboxamide (**4**). Both products were formed by using substrate/amine ratio of 1:1 and 1:2. The conversion was kept at about 50% in order to ensure the possibility of kinetic resolution of BINAM. Under these con-

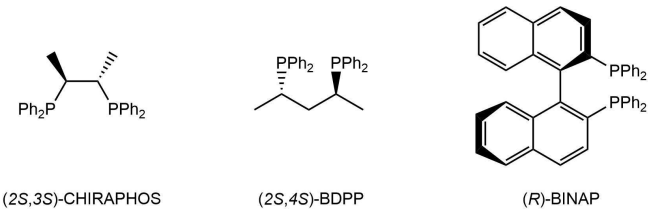
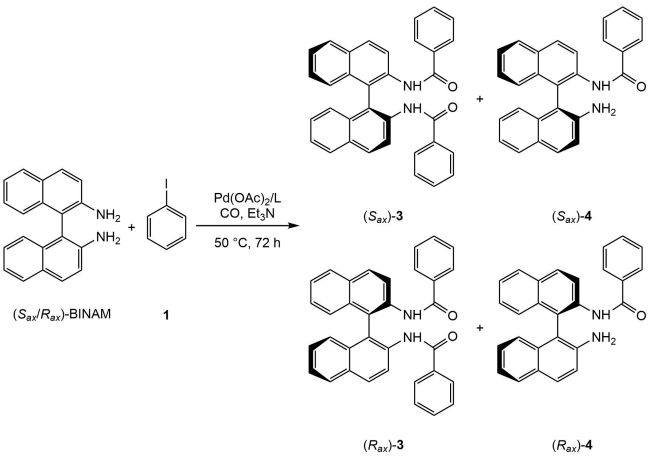


Figure 1. Chiral bidentate ligands used in aminocarbonylation.



Scheme 2. Aminocarbonylation of iodobenzene (**1**) in the presence of (R_{ax}/S_{ax})-BINAM (racemic) as *N*-nucleophile (L = 2 PPh_3, (*2S,3S*)-CHIRAPHOS, (*2S,4S*)-BDPP, (R_{ax})-BINAP).

ditions, the **3**/**4** ratio was influenced by the phosphine. In this way, the ratio was varied between 36:64 and 49:51 when substrate/amine ratio was kept at 1:1, and between 40:60 and 62:38 when substrate/amine ratio was kept at 2:1. Although the **3**/**4** chemoselectivities are rather low, it is worth to mention that the formation of the monocarboxamide **4** is favoured in the presence of the CHIRAPHOS ligand, able to form 5-membered chelate ring.

In case of **3** close to racemic mixtures were obtained with CHIRAPHOS. Low but measurable kinetic resolution was observed with (*2S,3S*)-BDPP and (*R*)-BINAP. Enantiomeric ratios of 45:55 and 46:54 were obtained, respectively (Table 1).

The aminocarbonylation of **2** was also carried out under the conditions proved to be most efficient for the transformation of **1** (Scheme 3). High chemoselectivity toward dicarboxamide **5** was observed, *i.e.*, practically no monocarboxamide was formed. Practically racemic mixtures were obtained in all cases.

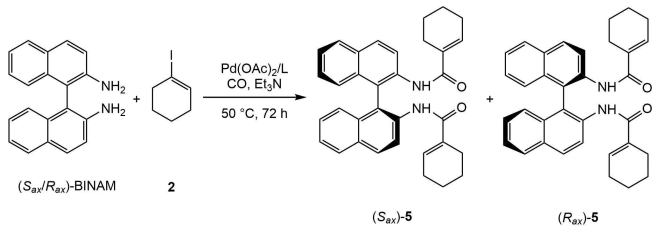
The most important observations regarding chemo- and enantioselectivity of the reaction influenced by the catalyst are as follows.

- Regarding chemoselectivity, the formation of dicarboxamide (**3**) is favoured by using BDPP- and BINAP-containing catalyst at a substrate:BINAM ratio of 2:1 even at low conversion. (The ratio of **3**/**4** are as follows: 57:43 (BINAP), 61:39 (BDPP), 40:60 (CHIRAPHOS).
- Using substrate:BINAM ratio of 1:1 the monocarboxamide (**4**) is slightly dominating. (The ratio of **3**/**4** are as follows: 49:51 (BINAP), 42:58 (BDPP), 36:64 (CHIRAPHOS).
- The monocarboxamide **4** can be synthesised and isolated as analytically pure compound using BDPP catalyst and substrate:BINAM ratio of 1:1.
- As mentioned above, enantiomeric enrichment of **3** can be achieved only with palladium catalysts bearing large bite-angle diphosphines such as BDPP (forming 6-membered chelate ring) and BINAP (forming 7-membered chelate ring).
- Since no perfect separation of the two enantiomers of **4** with chiral HPLC was achieved, the exact enantiomeric composition could not be determined. However, based on the line-shape analysis, the enantioselectivity is definitely below 10% in all cases.

Table 1. The ratio of dicarboxamide (**3**) enantiomers obtained in the aminocarbonylation of (R_{ax}/S_{ax})-BINAM[a].

1 / (R_{ax}/S_{ax})-BINAM	Ligand	(R_{ax})-**3**/ (S_{ax})-**3**[b]	**3**/**4**
1:1	PPh_3	50:50	40:60
1:1	(2*S*,3*S*)-CHIRAPHOS	50:50	36:64
1:1	(2*S*,4*S*)-BDPP	45:55	42:58
1:1	(*R*)-BINAP	46:54	49:51
2:1	PPh_3	50:50	62:38
2:1	(2*S*,3*S*)-CHIRAPHOS	50:50	40:60
2:1	(2*S*,4*S*)-BDPP	50:50	61:39
2:1	(*R*)-BINAP	50:50	57:43

a) Reaction conditions: $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol) or diphosphine (0.025 mmol), iodobenzene (1) (1 mmol), 2,2′-diamino-1,1′-binaphthalene (0.5 or 1 mmol), Et_3N (0.5 mL), DMF (10 mL), CO (1 bar), 50 °C.
b) Determined by chiral HPLC (See Supporting Information).

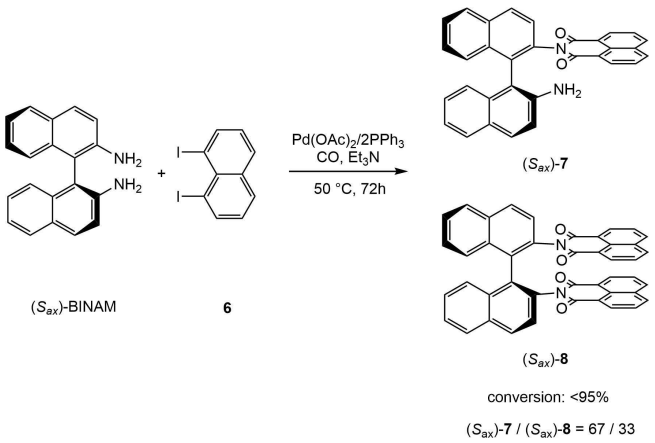


Scheme 3. Aminocarbonylation of 1-iodocyclohexene (**2**) in the presence of (R_{ax}/S_{ax})-BINAM.

Aminocarbonylation of 1,8-diiodonaphthalene (6) in the presence of (S_{ax})-BINAM as N-nucleophile

To check the possibility of imide formation using BINAM, the aminocarbonylation of 1,8-diiodonapthalene was investigated. As above, the *in situ* generated palladium(0) catalytic system was used. While the starting BINAM was practically fully converted, the formation of two products, **7** and **8** (in a ratio of 67/33) was observed. (Scheme 4). Compound **8** was isolated in analytically pure form, while **7** was identified only as a minor component in a 30:70 mixture of **7**:**8**. It has to be noted that a similar imide formation was already investigated with primary monoamines.[9]

The aminocarbonylation of **6** was also carried out with (R_{ax}/S_{ax})-BINAM in the presence of the chiral ligands above ((*2S,3S*)-CHIRAPHOS, (*2S,4S*)-BDPP, (R_{ax})-BINAP) Practically racemic mixtures were obtained in all cases except to BDPP, where slight enantiomeric enrichment of **7** (R_{ax})-**7**/(S_{ax})-**7** = 47/53) can be achieved. As above, no perfect base-line separation of the two enantiomers of **8** with chiral HPLC could be achieved. However, based on the line-shape analysis, the enantioselectivity is definitely below 3% in all cases.



Scheme 4. Aminocarbonylation of 1,8-diiodonaphthalene (**6**) in the presence of (S_{ax})-BINAM.

Conclusions

In the present study, initiated by the catalytic novelty of carrying out enantioselective reactions in aminocarbonylation, the synthesis of BINAM-based carboxamides was carried out. In addition to the enantiomerically pure mono- and dicarboxamides, obtained with enantiomerically pure BINAM, the enantiomerically enriched carboxamides were synthesised from racemic BINAM in the presence of palladium-enantiomerically pure chiral diphosphine catalysts. The asymmetric induction proved to be very low in all cases (up to 10%).

Supporting Information Summary

The Supporting Information is available free of charge on the website at

- description of the experiments, characterization of the products
- ^{1}H and ^{13}C NMR of the products, chiral HPLC conditions, chiral HPLC chromatograms.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: axial chirality · carbon monoxide · carbonylation · carboxamide · palladium.

[1] a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318–3326; b) A. Schoenberg, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327–3331; c) A. Schoenberg, R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 7761–7764.

[2] a) B. Cornils, W. A. Herrmann (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, **1996**; b) M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis (Vol. I–II.)*, Wiley-VCH, Weinheim, **1998**; c) H. M. Colquhoun, D. J. Thompson, M. V. Twigg, *Carbonylation. Direct Synthesis of Carbonyl Compounds*. Plenum Press, New York and London, **1991**; d) A. Arcadi, *Carbonylation of Enolizable Ketones (Enol Triflates) and Iodoalkenes* (Chapter 9) in Modern Carbonylation Methods (Ed. L. Kollár, Wiley-VCH, Weinheim, **2008**, 223–250.

[3] a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1–35; b) S. Roy, S. Roy, G. W. Gribble, *Tetrahedron* **2012**, *68*, 9867–9923; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009; d) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177–2250; e) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515–5548; f) C. F. J. Barnard, *Organometallics* **2008**, *27*, 5402–5422; g) R. Skoda-Földes, L. Kollár, *Curr. Org. Chem.* **2002**, *6*, 1097–1119; h) S–T. Gadge, B. M. Bhanage, *RSC Adv.* **2014**, *4*, 10367–10389.

[4] a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2002**, *16*, 9750–9753; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133 and references cited therein.

[5] a) R. M. B. Carrilho, M. M. Pereira, M. J. S. M. Moreno, A. Takács, L. Kollár, *Tetrahedron Lett.* **2013**, *54*, 2763–2765; b) G. Mikle, B. Boros, L. Kollár, *Tetrahedron: Asymmetry* **2014**, *25*, 1527–1531; c) R. M. B. Carrilho, A. R. Almeida, M. Kiss, L. Kollár, R. Skoda-Földes, J. M. Dabrowski, M. J. S. M. Moreno, M. M. Pereira, *Eur. J. Org. Chem.* **2015**, 1840–1847.

[6] J. Blum, D. Gelman, Z. Aizenshtat, S. Wernik, H. Schuman, *Tetrahedron Lett.* **1998**, *39*, 5611–5614.

[7] Some recent papers from our laboratory on the aminocarbonylation of iodoalkenes: a) G. Mikle, B. Boros, L. Kollár, *Tetrahedron: Asymm.* **2017**, *28*, 1733–1738; b) M. Gergely, L. Kollár, *Tetrahedron* **2017**, *73*, 838–844; c) G. Mikle, B. Boros, L. Kollár, *Tetrahedron: Asymmetry* **2016**, *27*, 377–383.

[8] a) C. Amatore, A. Jutand, M. A. M'Barki, *Organometallics* **1992**, *11*, 3009–3013; b) C. Amatore, E. Carre, A. Jutand, M. A. M'Barki, G. Meyer, *Organometallics* **1995**, *14*, 5605–5614; c) Z. Csákai, R. Skoda-Földes, L. Kollár, *Inorg. Chim. Acta* **1999**, *286*, 93–97 and references cited therein.

[9] A. Takács, P. Ács, L. Kollár, *Tetrahedron* **2008**, *64*, 983–987.

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