NOVEL CARBAMATE-BASED *P,O*-LIGANDS FOR ASYMMETRIC ALLYLIC ALKYLATIONS

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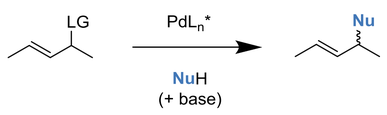
ABSTRACT

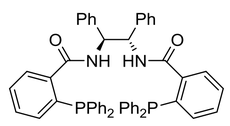
Highly funtionalized allylic compounds are invaluable intermediates for the pharmaceutical and agricultural industries. Since the early discovery of *B. Trost* and *J. Tsuji*, the field of Pd-catalysed asymmetric allylic alkylation (AAA) was growing rapidly. Due to its indisputible advantages such as mild reaction conditions and operational simplicity it is still one of the most relevant strategy for the synthesis of substituted allylic compounds [1]. One current state-of-art ligand family (*Trost-type ligands*) relies on a chiral diamine core using a *P,P*-bidentate motif for strong Pd-complexation, resulting in high catalytic activity and selectivity [1]. While such ligands are well estabilished and studied, monophosphine analogues with *P,O*-chelation did not gain much attention.
Herein, we report the synthesis of novel, chiral diamine-based *P,O*-ligands and their successful application in asymmetric allylic alkylations (AAA). After optimization of the reaction conditions, excellent yield and ee values have been obtained for aromatic and aliphatic substrates. The results show that such a new chelation concept can compete or even outperform the current state-of-art catalyst systems.

1. Asymmetric allylic alkylation

Palladium-catalysed asymmetric allylic alkylation (AAA) provides an efficient and convenient alternative for the synthesis of highly substituted allylic intermediates. A wide range of allylic compounds can be reacted with a variety of soft nuclephiles under mild reaction conditions:



LG: leaving group (OAc,OTs, OCOOR, OCOR...)
NuH: soft nuclephile (malonates, 1° and 2° amines...)
L_n*: chiral ligand



Scheme 1. General scheme of the Trost-Tsuji allylation (left) and a typical *Trost-type P,P*-bidentate ligand (right)

Based on various reports on the *Trost-type ligands,* it has been found that the two phosphine units are mainly responsible for the complex formation (*Figure 1, left*), however, a competition between the pure *P,P*-binding and *P,O*-chelation (*Figure 1, left*) is frequently mentioned as a major source of the limited enantioselectivity [2].
Enspired by these shortcomings and by our previous success with carbamate-based ligands in transition-metal catalysis [3], we aimed for the synthesis of novel *P,O*-monophosphine ligands for asymmetric allylic alkylation (Figure 1, right).

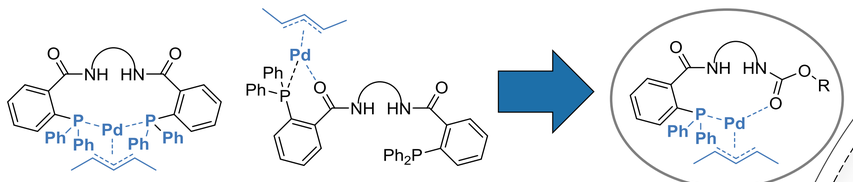
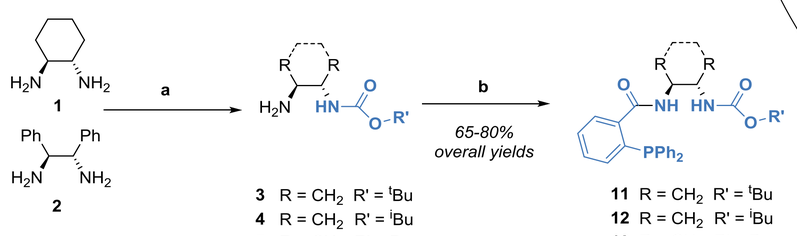


Figure 1. Competing chelation mode in common state-of art ligand systems (left) and our new concept with carbamate-based monophosphine ligands (right)

2. Ligand design

Starting from relatively cheap and easily accessible chiral pool of diamines **(1**-**2)**, a small library of carbamate-protected monophosphine ligands (**11**-**18**) was synthesized following a straightforward two-step procedure (*Scheme 2.*). After monoprotection of the diamines **1**-**2** [3], the monophosphine unit was introduced *via* DCC/DMAP coupling. After purification, ligands **11**-**18** were obtained with good overall yields.



1 **2**

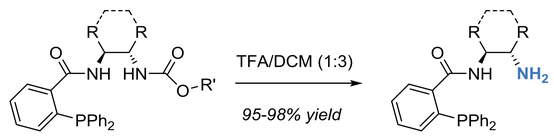
3 R = CH_2 R' = ^{t}Bu
4 R = CH_2 R' = ^{i}Bu
5 R = CH_2 R' = Bn
6 R = CH_2 R' = Ph
7 R = Ph R' = ^{t}Bu
8 R = Ph R' = ^{i}Bu
9 R = Ph R' = Bn
10 R = Ph R' = Ph

11 R = CH_2 R' = ^{t}Bu
12 R = CH_2 R' = ^{i}Bu
13 R = CH_2 R' = Bn
14 R = CH_2 R' = Ph
15 R = Ph R' = ^{t}Bu
16 R = Ph R' = ^{i}Bu
17 R = Ph R' = Bn
18 R = Ph R' = Ph

Reagents and conditions: (a): anhydride/chloroformate in MeOH (b): 2-PPh_2-PhCOOH, DCC/DMAP, anhydr. CH_2Cl_2

Scheme 2. Design of novel carbamate-based monophosphine ligands

In order to experimentally investigate wheather the carbamate carbonyl group plays a crucial role in the complexation, the unprotected analogues of compound **11** and **15** have been also synthesized:



11 R = CH_2 R' = ^{t}Bu
15 R = Ph R' = ^{t}Bu

19 R = CH_2
20 R = Ph

Scheme 3. Deprotection procedure for compounds **11** and **15**

3. Parameter optimization and ligand screening

After the successful synthesis and characterization of ligands **11-20**, their catalytic activity and selectivity was investigated in the AAA reaction of (±)-diphenylallyl acetate **(21)** and dimethyl malonate:

21

Scheme 4. AAA reaction of (±)-diphenylallyl acetate **(21)** and dimethyl malonate

- The use of chlorinated solvent results in high acivity but moderate ee
- Higher ee in ether type solvents, specially in diethyl ether
- Toluene also results in excellent ee, albeit moderate reactivity

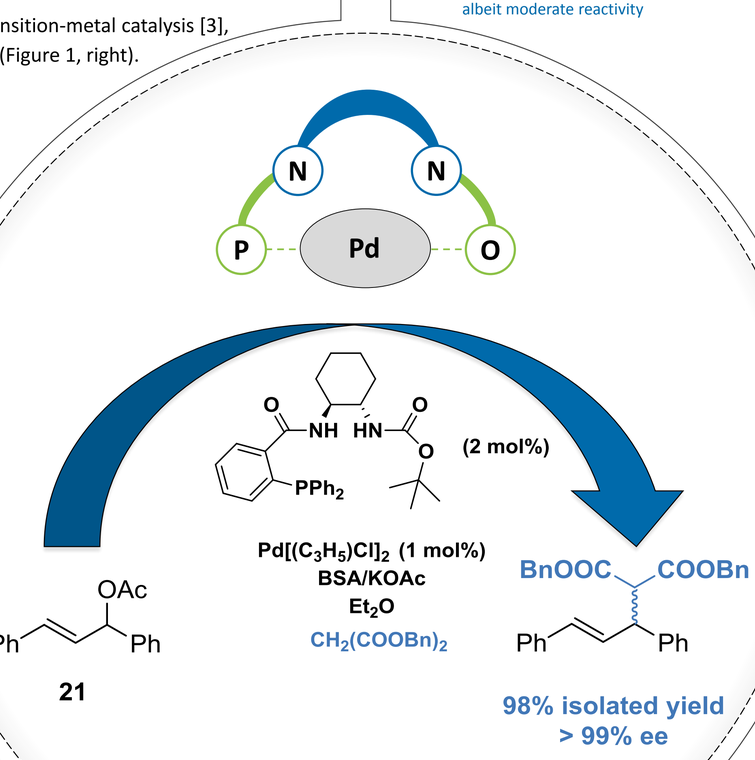
Solvent screening

Entry	Solvent	Yield [%]	ee [%]
1	CH_2Cl_2	95	49 (*R*)
2	EtOAc	55	70 (*R*)
3	THF	89	73 (*R*)
4	MTBE	93	75 (*R*)
5	**Et_2O**	**94**	**>99 (*R*)**
6	Toluene	57	99 (*R*)

Ligand screening

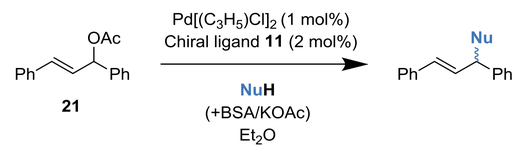
Entry	Ligand	Yield [%]	ee [%]
1	**11**	**94**	**>99 (*R*)**
2	**12**	83	85 (R)
3	**13**	67	81 (*R*)
4	**14**	70	75 (*R*)
5	**15**	87	65 (*R*)
6	**16**	85	62 (*R*)
7	**17**	54	56 (*R*)
8	**18**	61	59 (*R*)
9	**19**	< 5	n.d.
10	**20**	< 5	n.d.

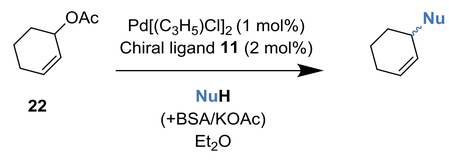
- The cyclohexyldiamine core was found to be superior over diphenylethylenediamine
- Slightly better results were obtained with non-aromatic carbamate units
- In case of non-aromatic carbamates, the presence of an extra CH_2-spacer is clearly not benefitial
- The carbamate-unit is necessary, as ligands **19** and **20** gave almost no reaction

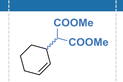
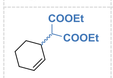
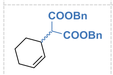
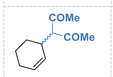
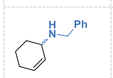


4. Scope and limitations

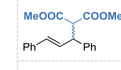
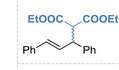
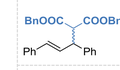
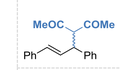
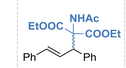
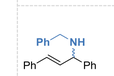
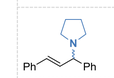
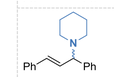
After identifying the optimal reaction conditions and the best ligand system, a series of different soft nucleophiles were used for the AAA reaction of (±)-diphenylallyl acetate (**21**) and (±)-3-acetoxycyclohexene (**22**).
Under the previously optimized reaction conditions, excellent enantioselectivities with high yields were observed for the AAA reaction of **21**, while the corresponding products of acetate **22** could be obtained with high yields and good to excellent ee values.





Entry	Product	Yield [%]	ee [%]
1		86	79 (*R*)
2		88	83 (*R*)
3		90	> 99 (*R*)
4		89	74 (*R*)
5		80	60 (*R*)

The π – π stacking between the ligand and the substrate seems to be necessary for high ee

Entry	Product	Yield [%]	ee [%]
1		93	> 99 (*R*)
2		94	99 (*R*)
3		98	> 99 (*R*)
4		89	95 (*R*)
5		98	92 (*S*)
6		87	95 (*S*)
7		98	92 (*S*)
8		96	86 (*S*)

5. Conclusion

Novel *P,O*-ligands with unique coordination mode have been synthesized in a staightforward two-step procedure with good overall yields. After parameter optimization, the carbamate-monophosphine ligand **11** was found to be an excellent catalyst for asymmetric allylic alkylations, providing high catalytic activities and good to excellent enantioselectivities for different substrates and nucleophiles.

[1] Trost, B. M. *Chem. Rev*. **1996**, *96*, 395.
[2] Lloyd-Jones, G. C.; Stephen, S. C.; Fairlamb, I. J. S.; Martorell, A.; Dominguez, B.; Tomlin, P. M.; Murray, M.; Fernandez, J. M.; Jeffery, J. C.; Riis-Johannessen, T.; Guerziz, T. *Pure. Appl. Chem*. **2004**, *76*, 589.
[3] Pálvölgyi, Á. M.; Bitai, J.; Zeindlhofer, V.; Schröder, C.; Bica, K. *ACS Sustainable Chem. Eng*. **2019**, *7*, 3414.

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