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“Clickphine”: A Novel and Highly Versatile P,N Ligand Class via Click Chemistry

Remko J. Detz, Silvia Arévalo Heras, R. de Gelder,† Piet W. N. M. van Leeuwen, Henk Hiemstra, Joost N. H. Reek,* and Jan H. van Maarseveen*

Van't Hoff Institute for Molecular Sciences, Faculty of Science, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands, and Molecular Materials, Institute for Molecules and Materials, Radboud University Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands

jvm@science.uva.nl; reek@science.uva.nl

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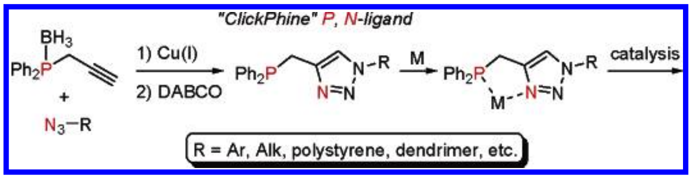
ABSTRACT



A novel P,N-type ligand family (ClickPhine) is disclosed that is easily accessible using the Cu(I)-catalyzed azide–alkyne “click” cycloaddition. A diverse set of ligands was made in just three steps from readily available starting materials to give several homogeneous and a heterogeneous catalyst. Preliminary experiments show the efficacy of these ligands in the Pd-catalyzed allylic alkylation reaction.

Transition metal catalysis is increasingly important both for industry and academia, since it provides new efficient and sustainable routes for organic synthesis and the production of fine chemicals.[1] Ligand variation is the most powerful tool in transition metal catalysis, and key features of transition metal catalysts such as activity, selectivity, and stability are dictated by the steric and electronic properties of ligands that are coordinated to the metal.[2] It is therefore no surprise that most effort in the area of catalysis is put into the design of novel ligands. Besides the development of new catalysts by ligand design and combinatorial approaches,[3] much research is devoted to catalyst recycling. Various elegant concepts for homogeneous catalyst separation and recycling have been developed[4] such as the use of ionic liquids,[5] supercritical fluids,[6] supported aqueous phase catalysis,[7] and fluorous phase catalysis.[8] A widely studied approach to facilitate catalyst−product separation is the attachment of homogeneous catalysts to dendritic,[9] polymeric organic, inorganic, or hybrid supports.[10] Here the ligand requires a group that enables anchoring to such a support.

Sharpless and co-workers recently introduced click-chemistry as a new way of categorizing organic reactions

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[†] Radboud University Nijmegen.

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that are modular in nature, highly efficient, mild, and selective and require only simple reaction and workup procedures.[11] We anticipated that the implementation of a click-reaction in the synthetic scheme of a ligand should automatically lead to a novel versatile ligand that is easy to vary. In addition, it might also provide a handle to attach the ligand to various supports.

We were especially interested in the Cu(I)-catalyzed 1,3-dipolar "click" azide−alkyne cycloaddition,[12] since the resulting 1,4-disubstituted 1,2,3-triazoles can be part of a bidentate P,N-type ligand. P,N ligands represent an important class of ligands that have been applied in various catalytic transformations.[13]

Recently, a triazole-based monophosphine, ClickPhos, was reported showing high activity in the Pd-catalyzed Suzuki−Miyaura coupling and amination reactions of aryl chlorides.[14] Also, the triazole itself has already shown its good metal-coordination properties.[15] Surprisingly, the use of triazoles as nitrogen donors in P,N ligands has, as far as we know, no literature precedent yet. This novel class of P,N ligands might be attractive because of the easy and highly modular synthetic accessibility, which enables facile tuning of their steric and electronic properties for catalyst optimization (Figure 1). In addition, several commonly used supports have azide or acetylene moieties facilitating a complete system approach including a catalyst-separation step underscoring their versatility.

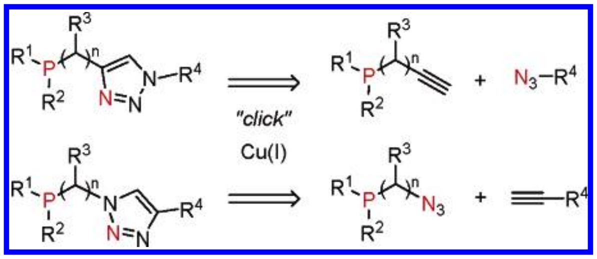
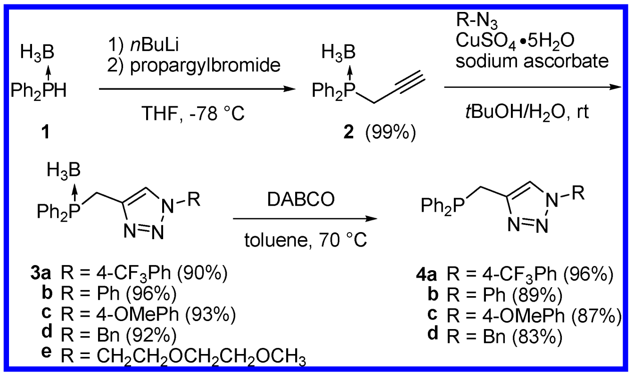


Figure 1. P,N ligands obtained by the Cu(I)-catalyzed azide−alkyne cycloaddition reaction.

In this paper, we report the preparation of a series of P,N ligands using click chemistry, and we show that this strategy allows facile immobilization of these ligands on soluble (dendrimers, poly(ethylene glycol)) and insoluble supports (polystyrene resin). Preliminary results show that the palladium catalysts are highly active and regioselective in the allylic alkylation of cinnamyl acetate and that the immobilized catalyst can indeed be recycled.

The synthesis of the first ligand commences with the treatment of commercially available borane-protected diphenylphosphine **1** with *n*-BuLi followed by addition of propargyl bromide providing propynyl phosphine **2** (Scheme 1).

Scheme 1. Synthesis of Ligand Derivatives **4a−e**



The acetylene moiety was subjected to Cu(I)-catalyzed azide−alkyne cycloaddition providing the P-protected ClickPhine derivatives **3a−e** in high yields. Throughout the sequence, the phosphine must be protected to prevent unwanted iminophosphorane formation (Staudinger reaction) during the "click" reaction. The unprotected ligands **4a−d** were obtained after liberation of the phosphine by treatment with DABCO.

Azidophosphine **6** was prepared starting from the previously reported hydroxyphosphine **5**.[16] Although the subsequent azide−alkyne cycloaddition was slower than the reversed one, several acetylenes could be coupled providing **7a−c**. Borane removal with DABCO provided ligands **8a−c**, which will be slightly different from **4** because these ligands will coordinate with N(2) instead of N(1) when the ligand functions as a bidentate ligand (Scheme 2).

To demonstrate that the approach indeed also works to arrive at supported ligands, both a dendrimer and a polystyrene resin were decorated with the ligands. The previously reported second-generation carbosilane dendrimer **9** employing an azide group at the focal point was attached to

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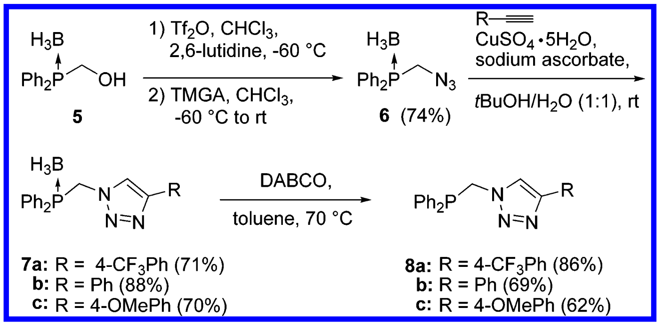
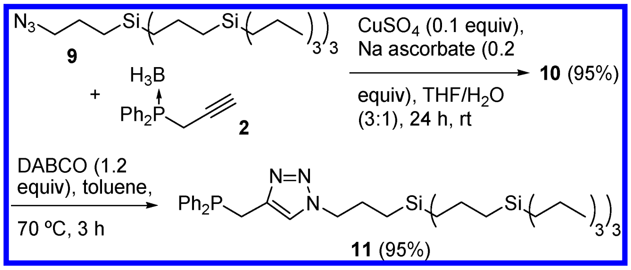
Scheme 2. Synthesis of Ligand Derivatives **8a−c**



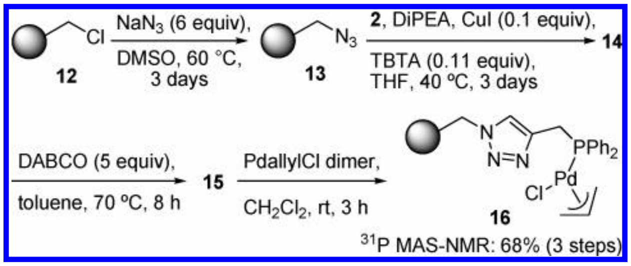
phosphine **2** using standard click conditions.[17] Deprotection of the phosphine with DABCO gave dendritic ligand **11** in very high yield (Scheme 3).

Scheme 3. Synthesis of the Dendritic Ligand **11**



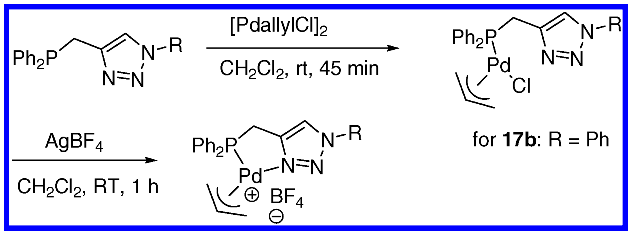
The polystyrene-supported azide was prepared by treatment of Merrifield resin **12** with sodium azide according to literature procedures (Scheme 4).[18] The resulting resin **13** was subjected to the Cu(I)-catalyzed cycloaddition with propynylphosphine **2** using tris(benzyltriazolylmethyl)amine (TBTA) as the ligand to accelerate the reaction.[15] The polystyrene-supported ligand complex **16** was obtained after DABCO-mediated phosphine liberation and subsequent complexation with palladium. ^{31}P MAS-NMR analysis revealed a yield of 68% of the supported complex. Next to the corresponding phosphine oxide (13%), two minor phosphorus signals (19%) of unidentified species were also detected.

Scheme 4. Synthesis of the Polystyrene-Supported Complex **14**



Upon mixing ligands **4a−d** or dendritic ligand **11** with $[Pd(allyl)Cl]_2$ in dichloromethane the corresponding neutral metal complexes are formed, according to NMR experiments (Scheme 5). The ^{1}H NMR spectra show broad signals for the allylic protons (except for the central proton) indicating isomerization via π rotation or π,σ-rearrangement. The ^{31}P NMR spectrum shows a broad signal at 20.6 ppm. Crystals suitable for X-ray analysis were obtained for complex **17b**, revealing monodentate binding of the ligand (Figure 2) with the chloride still coordinated to the palladium.[19]

Scheme 5. Synthesis of Palladium Complexes



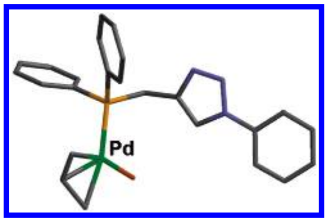


Figure 2. X-ray diffraction structure of complex **17b**. Hydrogen atoms have been ommited for clarity.

The corresponding cationic palladium−allyl complexes were prepared from the palladium chloride by addition of $AgBF_4$. The ^{1}H NMR signal of the triazole proton shifted 0.71 ppm to lower field (from 8.15 to 8.86 ppm) after ion-exchange, and the CH_2 group gave rise to an AB pattern showing that these protons became inequivalent. In addition, the signal in the ^{31}P NMR spectrum shifted from 20.6 to 40.5 ppm and became sharper. These data all point to the formation of a palladium−allyl complex in which the ligand shows bidentate P,N coordination. Unfortunately, all crystallization attempts of these complexes failed.

Many efforts have been made in enantioselective allylic alkylation with P,N-ligands;[20] the subject of regioselectivity

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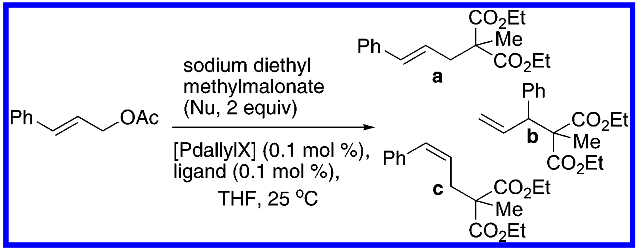
(19) CCDC 603618 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK.; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk). The crystallographic data are also available in the CIF file in the Supporting Information.

(20) For a seminal example, see: Pretot, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323.

has been less studied.[21] Our initial experiments show that the palladium complexes of the novel ligands described are active in the Pd-catalyzed allylic alkylation of cinnamyl acetate applying sodium methyl diethylmalonate as nucleophile. The palladium complexes are highly active and selective for the trans product **a** (Table 1), and all reactions went to completion after prolonged reaction. We previously studied the effect of the bite angle of P,N-type ligands on the selectivity in the palladium-catalyzed allylic alkylation, and we found that large bite angle ligands resulted in preferential formation of the branched product.[22] The ligands that are reported here have small bite angles and provide very high selectivities for the linear product (up to 98%).[23] Interestingly, within the small ligand series investigated we already observed a large effect in the reactivity. The catalysts based on ligands **4d** and **11** (the dendritic ligand), with more electron-rich triazole rings, were considerably more active (entries 4 and 5). It was also observed that the cationic palladium complexes generally gave higher initial rates than the neutral analogues.

Table 1. Pd-Catalyzed Allylic Alkylation of Cinnamyl Acetate



			conversion[a] (%)		selectivity[a,b] (%)	
	ligand	X	35 min	1 h	**a**	**b**
1	**4a**	BF_4	55	65	97	3
2	**4b**	BF_4	54	68	97	3
3	**4c**	BF_4		78	97	3
4	**4d**	BF_4	78	90	98	2
5	**11**	BF_4	80	91	98	2
6[c]	**15**	Cl	64	72	96	4
7[c,d]	**15**	Cl		54	96	4

[a] Conversion of cinnamyl acetate and regioselectivity were determined by GC using decane as internal standard and in select cases confirmed by NMR. All reactions gave full conversion. [b] No cis product (**c**) was observed. [c] Approximately 2 mol % of catalyst and 1:0.7 cinnamyl acetate/Nu ratio. [d] The reaction was carried out with the **15**−Pd complex recovered after three previous runs without further addition of $[PdallylCl]_2$.

Preliminary experiments with polystyrene-supported catalyst **16** showed that the supported catalyst retained its activity and was easy to recycle. A small decrease in activity upon recycling had to be accepted; the fourth run still gave 54% conversion of the cinnamyl acetate after 1 h reaction time, whereas the first run showed 72% conversion (Table 1, entries 6 and 7), which is not uncommon for palladium catalysts.

In conclusion, we have shown the versatility of a new class of P,N-ligands that is accessible via the robust Cu(I)-catalyzed alkyne−azide cycloaddition enabling facile tailor-made modification for optimization or other (e.g., ligand immobilization) purposes. The efficacy of these ligands is shown for Pd-catalyzed alkylation reactions.

Acknowledgment. The NRSC-C is kindly acknowledged for financial support of this project.

Supporting Information Available: The crystallographic CIF file of **17b** and full experimental details and compound characterization data for **2**, **3a**−**e**, **4a**−**d**, **6**, **7a**−**c**, **8a**−**c**, **10**, **11**, and **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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