Looking for a Synergic Effect between NHCs and Chiral P-Ligands

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ABSTRACT

The issue of the added value of NHCs in asymmetric catalysis with respect to trusted chiral P-ligands was addressed: considering a prototypical asymmetric allylic alkylation reaction as a model, the association of a priori inhibiting and achiral NHCs with modular P-ligand resulted in enhancement of er up to 508% and increased rates.

During the past decade, N-heterocyclic carbenes (NHCs) have emerged as extremely powerful and versatile ligands for transition metals in organometallic catalysis, with tremendous applications in organic synthesis.¹ This popularity is commonly attributed to an unprecedented set of properties: their electron-rich nature, their tight binding to the metal, their original shape and resulting steric bulk.¹ Although they are sometimes presented as "superior equivalents of phosphines", which are more labile and/or π -acceptor ligands, a more objective statement would rather emphasize

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the complementarities of these two families. In 1998, Rösch et al. already pointed out the theoritical potentiality of bidentate ligands featuring these two functionalities.^{2a} Since then bidentate P-NHC ligands, as well as catalytic systems mixing both a monodentate phosphine and a NHC, have been extensively applied in catalysis.²⁻⁴ The NHC is usually considered as the key partner. The P-ligand is mainly proned

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to leave the metal center in order to initiate the catalytic cycle. However it can play a more active role, by joining back and assisting the metal in another key elemental step, such as reductive elimination. The reality of such a synergic effect was recently unambiguously demonstrated in nickel-catalyzed reactions.⁵

As recently stated,^{6c} NHCs are far from outclassing the popular P-ligands in asymmetric organometallic catalysis.⁶ One reason for this low success rate may lie in the particular optimization of chiral catalysts, which cannot usually be dissociated from a serendipitous search for key structural features through screening of collections of ligands. Indeed, NHCs are far from matching the enormous structural diversity of their phosphorus analogues.⁷ Thus, bidentate P-NHCs, which would meet the attractive electronic and steric properties of NHCs and would also benefit from successful decades of innumerable studies in designing chiral phosphines, should have emerged as a powerful class of chiral ligands. But strikingly, they have generally yielded poor results.⁸

In this paper, we address the issue of the added value of NHCs in asymmetric catalysis, with respect to trusted chiral P-ligands. Focusing on the critical need of chiral NHCs for structural diversity, we considered an alternative strategy based on the combination⁹ of monodentate NHCs with highly tunable monodentate chiral P-ligands. Herein, we validate this approach for a specific model reaction by reporting the proof of a synergic effect between these two partners.

As a model reaction, we chose the prototypical asymmetric palladium-catalyzed allylic alkylation (AAA)¹⁰ of 1,3-diphenylallylacetate **1** by dimethyl malonate **2** because it perfectly illustrates the paradoxical statement that initiated our study. Indeed P-NHC ligands have already been tested in AAA,^{8g-i} but they afforded poor enantiomeric excesses (ee's), whereas a synergic effect between a phosphine and such a strong σ -donor partner would have been expected.¹¹ Among the numerous chiral P-ligands that have already proven their

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efficiency in AAA, we focused on modular 1,3,2-diazaphospholidines^{12–13} and chose ligands $4\mathbf{a}-\mathbf{f}$ as standards. We completed that small library with a set of classical monodentate NHCs $5\mathbf{a}-\mathbf{e}$ and related bidentate P-NHCs $6\mathbf{a},\mathbf{b}$ (Scheme 1).



Monodentate chiral ligands 4a-f were engaged in the palladium-catalyzed AAA in standard conditions. As expected, the reaction was completed within 1–3 h at 0 °C in dichloromethane. Compound 3 was obtained with excellent isolated yields and with ees ranging from 26% to 82% (Table 1, entries 1–6). In marked contrast, classical NHCs **5a,b** are unefficient because their strong σ -donation decreases the

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Table 1. Chiral 1,3,2-Diazaphospholidines **4a**–**f** and Bidentate P-NHCs **6a,b** as Ligands for the Palladium-Catalyzed AAA

Ph Ph Ph	+ MeO 2	$ \begin{array}{c} $	gand IIIyI)) ₂ 0,5 equiv) cONa Mo , CH ₂ CI ₂ Ph	eo Ph (-)-S-3
$entry^a$	ligand	temp (°C)	yield $(\%)^b$	ee (%) ^c
1	4a	0	86	82
2	4b	0	91	62
3	4c	0	89	23
4	4d	0	98	74
5	4e	0	92	53
6	4f	0	99	77
7	6a	0	47^d	89
8	6b	0	21^d	79
9	6a	25	95	80
10	6b	25	92	71

^{*a*} See Supporting Information for experimental details. ^b Yield after purification. ^c Determined by chiral HPLC on a OD-H Chiracel column. ^{*d*} Conversion after 48 h, determined by ¹H NMR.

electrophilicity of the key π -allylpalladium intermediate.¹⁴ In our condition, they afforded negligible conversions (less than 1%) after 2 days, even at room temperature. This deactivating effect can be partly compensated by associating the NHC with a more acceptor partner¹⁵ or by increasing its steric bulk.14 Thus, NHC-substituted diazaphospholidines **6a,b**, which were generated in situ from the corresponding imidazolium or imidazolidinium salts and butyllithium, proved to be active ligands for the formation of 3. However, despite an improved ee of 89% (ligand 6a, entry 7), the reaction rates remained modest when compared with the parent monodentate diazaphospholidines 4a-f. Indeed, the half reaction times were at minimum 2 days at 0 °C (Table 1, entries 7 and 8). At 25 °C, total conversions were obtained within 2 days (entries 9 and 10). The enantioselectivities (71-80% ee) were the highest ever obtained to date for that reaction with a chiral P-NHC ligand. However, they did not exceed the 82% ee obtained with ligand 4a.

We considered that NHCs **6a,b** do not feature a so significant steric hindrance because they are related to 1-mesityl-3-methylimidazol-2-ylidene **5c**. This assumption was supported by the report of Hodgson et al. that tuning the single N-substituent of a bidentate P-NHC ligand was not sufficient to affect the reaction rate.^{8g} Thus, expecting a more significant synergic effect, we associated monodentate NHCs **5a**–**e**, generated in situ from the corresponding tetra-fluoroborate imidazolium (or imidazolidinium) salt, with P-ligand **4a**.

As shown in Figure 1, the use of monodentate NHCs clearly exacerbated the effect of the steric hindrance on rates.



Figure 1. Synergic effect between monodentate NHCs and P-Ligand 4a: kinetics of the palladium-catalyzed allylic alkylation of 1 by 2 in CH_2Cl_2 at 0 °C.

The combination of 1-mesityl-3-methylimidazol-2-ylidene **5c** with **4a** (series d) afforded a slow rate, similar to bidentate P-NHC **6a** (series g). On the other hand, when replacing the methyl group of **5c** by bulkier substituents, the AAA proceeded in few hours in CH₂Cl₂ at 0 °C (series b, c, e, f), so that it could even exceed the rate observed with **4a** alone (series a). With 1,3-di-*tert*-butyl- or 1,3-di-1-adamantyl imidazolidenes **5b,d**, the addition of a priori deactivating σ -donor NHCs resulted in fine in doubling the reaction rate. Interestingly, **5e** inhibited the reaction (series f). This is in agreement with the general assumption that imidazolidin-2-ylidenes are more σ -donating than corresponding imidazol-2-ylidenes.¹⁶⁻¹⁷

We then turned our attention to enantioselectivities, and investigated 22 combinations between diazaphospholidines **4a**-**f** and NHCs **5a,b,d,e**.

As shown in Table 2, compound **3** was obtained in few hours at 0 °C in CH₂Cl₂, with good isolated yields and enantioselectivities ranging from 47% (ligands **4c** and **5e**, entry 21) to 95.2% (ligands **4d** and **5a**, entry 4). In every case, (-)-*S*-**3** remained the major enantiomer. Importantly, the combination of a NHC with a diazaphospholidine resulted in better ee's, compared to the same P-ligand alone. The structural diversity, which arose from the replacement of bidentate P-NHCs by combinations of corresponding monodentate ligands, is then a key advantage. Starting from *m* cheap and easily available NHCs and *n* chiral modular P-ligands, up to *n*•*m* chiral catalysts bearing NHCs could be screened, thus increasing the probability of discovering a "hit".

As a matter of fact, although enantiomeric excess is a popular descriptor of enantiomer composition, er is by far more suitable because it directly reflects the relative rates

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 Table 2.
 A Combinatorial Approach: Mixtures of Chiral

 P-Ligands 4a-f with NHCs 5a,b,d,e

OAc	+ MeO	0 ^{5 %}	(CIPd(allyl)) ₂ 0,5 equi AcONa		
1	2	ONIC	20, 1, 0, 0, 01,20,2	(-)-S- 3
$entry^a$	P-ligand	NHC	yield $(\%)^b$	er^{c}	ee (%)
1	4a	5a	96	13.0	86
2	4b	5a	93	6.4	73
3	4c	5a	84	2.8	48
4	4d	5a	84	40.7	95.2
5	4e	5a	88	5.8	71
6	4f	5a	92	8.5	79
7	4a	5b	78	14.6	87
8	4b	5 b	94	8.0	78
9	4c	5b	94	3.1	51
10	4d	5b	89	13.8	86
11	4e	5b	82	8.7	79
12	4f	5b	89	12.3	85
13	4a	5d	96	26.4	93
14	4b	5d	98	7.6	77
15	4c	5d	96	3.1	51
16	4d	5d	93	8.8	80
17	4e	5d	78	8.9	80
18	4a	5e	93	12.0	85
19	4a	$\mathbf{5e}^d$	90	11.7	84
20	4b	$\mathbf{5e}^d$	82	8.2	78
21	4c	$\mathbf{5e}^d$	81	2.8	47
22	4d	$\mathbf{5e}^d$	70	19.6	90
23	4e	$\mathbf{5e}^d$	92	11.3	84

^{*a*} See Supporting Information for experimental details. ^{*b*} Yield after purification. ^{*c*} Determined by chiral HPLC on a OD-H Chiracel column. ^{*d*} NHC generated in situ from the corresponding imidazolidinium hexafluorophosphate salt.

that determine the enantioselectivity of asymmetric reactions.¹⁸ In order to address more precisely the issue of the added value of the NHC ligand, we considered τ , the enhancement of enantiomeric ratio of product **3**, as a measure of the synergy between NHCs **5** and diazaphospholidines **4** on enantioselectivity ($\tau = [\{\text{er with ligand } 4\} \times 100)$). As shown in Figure 2, addition of a NHC frequently resulted in an enhancement of er ranging from 50% to 120%. Seven combinations afforded $\tau > 150\%$, a maximal synergic effect ($\tau = 508\%$) being reached with ligands **5a** and **4d**.



Figure 2. Synergic effect on enantioselectivity: enhancement of enantiomeric *ratio*.

Importantly, **5a** and **4d** afforded also the best absolute enantioselectivity (95.2% ee, which corresponds to 40.7 er), whereas initially **4d** was not the best chiral 1,3,2-diazaphospholidine (see Table 1, entries 1-6). In addition, the most efficient combinations of NHCs and diazaphospholidines are displayed in Figure 2 in an apparent random fashion, so that the effect of added NHCs on enantioselectivity clearly resulted in subtle stereoelectronic factors that could not be easily modelized. Such statements indicate a posteriori the relevance of a combinatorial approach.

In conclusion, we have demonstrated the paradoxical added value of a priori deactivating and achiral NHCs in a particular case study. The association of a strong σ -donor ligand with chiral 1,3,2-diazaphospholidines led to an improvement of enantioselectivity, and the resulting inhibition of the catalytic system could be compensated by a significant steric hindrance around the metal center. In principle, this combinatorial approach could be generalized to a broad range of asymmetric organometallic catalytic processes that would benefit from the key features of NHCs (strong σ -donation and/or the steric bulk) and the structural diversity of modular chiral P-ligands. Indeed, because of the lability of the latter, compared to the tight binding of NHCs to metals, the main prerequisite for such cooperation is the ability of the chiral P-ligand to coordinate the metal at the enantioselective step of the mechanism.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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