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

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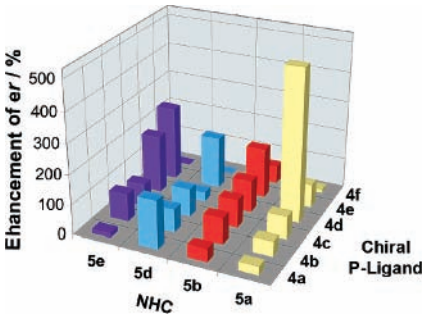
ABSTRACT



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 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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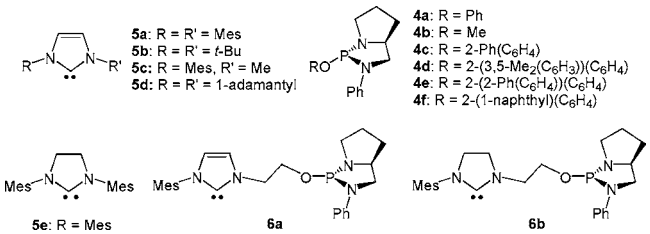
to leave the metal center in order to initiate the catalytic cycle. However it can play a more active role, by joining back and assisting the metal in another key elemental step, such as reductive elimination. The reality of such a synergic effect was recently unambiguously demonstrated in nickel-catalyzed 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 combination[9] 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 efficiency in AAA, we focused on modular 1,3,2-diazaphospholidines[12−13] and chose ligands **4a**−**f** as standards. We completed that small library with a set of classical monodentate NHCs **5a**−**e** and related bidentate P-NHCs **6a,b** (Scheme 1).

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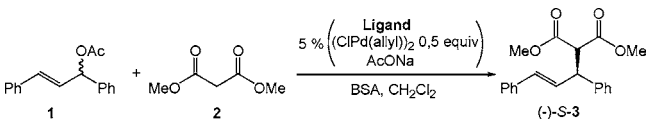
Table 1. Chiral 1,3,2-Diazaphospholidines **4a**−**f** and Bidentate P-NHCs **6a,b** as Ligands for the Palladium-Catalyzed AAA



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 ^{1}H 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 partner[15] 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 tetrafluoroborate 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.

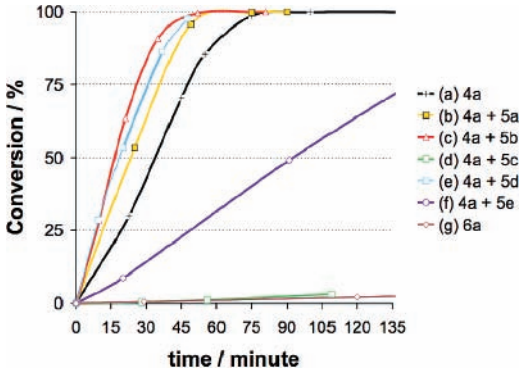


Figure 1. Synergic effect between monodentate NHCs and P-Ligand **4a**: kinetics of the palladium-catalyzed allylic alkylation of **1** by **2** in CH_2Cl_2 at 0 °C.

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 CH_2Cl_2 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 CH_2Cl_2, 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 $n \cdot m$ 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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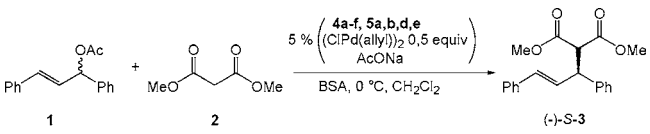
(17) A similar trend was observed for P-NHCs **6a** and **6b** (see Table 1, entries 7 and 8). However, differences between imidazolidin-2-ylidenes and imidazol-2-ylidenes are not always so significant, and their interpretation could be puzzling; see for example: (a) Herrmann, W. A.; Schütz, J.; Frey, G. D.; Herdtweck, E. *Organometallics* **2006**, *25*, 2437−2448. (b) Diez-Gonzales, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874−883.

Table 2. A Combinatorial Approach: Mixtures of Chiral P-Ligands **4a**−**f** with NHCs **5a**,**b**,**d**,**e**



1 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**	**5b**	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**	**5e**[d]	90	11.7	84
20	**4b**	**5e**[d]	82	8.2	78
21	**4c**	**5e**[d]	81	2.8	47
22	**4d**	**5e**[d]	70	19.6	90
23	**4e**	**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 (τ = [{er with ligands **4** and **5**}−{er with ligand **4**}]/{er with ligand **4**} × 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 τ > 150%, a maximal synergic effect (τ = 508%) being reached with ligands **5a** and **4d**.

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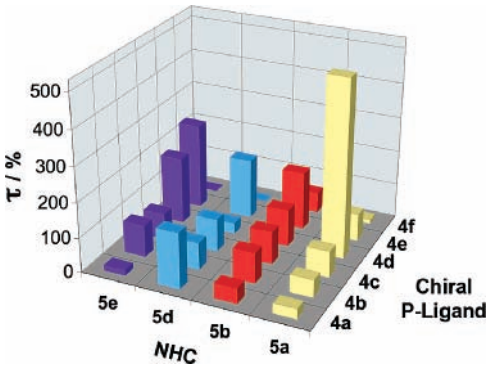

Figure 2. Synergic effect on enantioselectivity: enhancement of enantiomeric *ratio*.

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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