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Design, Preparation, and Implementation of an Imidazole-Based Chiral Biaryl P,N-Ligand for Asymmetric Catalysis

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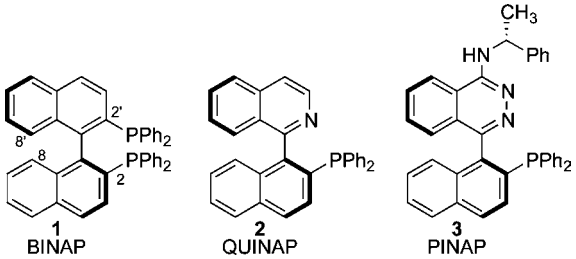
Supporting Information

ABSTRACT: A new strategy for increasing the barrier to rotation in biaryls has been developed that allows for the incorporation of 5-membered aromatic heterocycles into chiral atropisomers. Using this concept, an imidazole-based biaryl P,N-ligand has been designed and prepared as a single enantiomer. This ligand performs exceptionally well in the enantioselective A^3-coupling, demonstrating the potential of this new design element.

The chiral biaryl structural motif is an important component found in a diverse array of catalysts for enantioselective synthesis.[1] Ligands built on the binaphthalene and biphenyl backbones are regularly employed in a variety of reactions, with such success that BINAP (**1**) and BINOL are referred to as privileged ligands.[2] The atropisomeric backbone in the vast majority of chiral biaryl ligands is comprised of substituted or fused benzenoid aromatics that rely on *ortho*-substitution to hinder rotation about the biaryl bond.[3] Although reducing the steric demand by removing substituents from the 2- or 8-position lowers the barrier to rotation and hence reduces configurational stability,[4] P,N-ligands such as QUINAP (**2**)[5] and PINAP (**3**)[6] have successfully been prepared and employed in enantioselective transformations.[7,8] It is well-known that changing the dihedral and bite angles of the biaryl can drastically affect ligand performance, and the success of **2** and **3** can be attributed to modifying these parameters as well as changing the donating properties of the ligand.[9]



Atropisomeric P,N-ligands have proven to be highly selective,[7] but making structural modifications for fine-tuning of the ligand is challenging, and relatively few derivatives are known.[8] In contrast to the substituted or fused 6-membered aromatics commonly encountered, 5-membered heteroaromatics would offer a new, unexplored chemical diversity and be much easier to prepare and modify using established methods.[10] One potential problem is that *ortho*-substituents on 5-membered rings are not held as closely in space to the adjacent aromatic group due to the modified bond angles of the ring system. This may lead to a reduced barrier to rotation and loss of chirality. In his seminal work, Brown encountered this difficulty when **4**, an indole version of QUINAP, was prepared and found not to be configurationally stable (Figure 1).[11] While

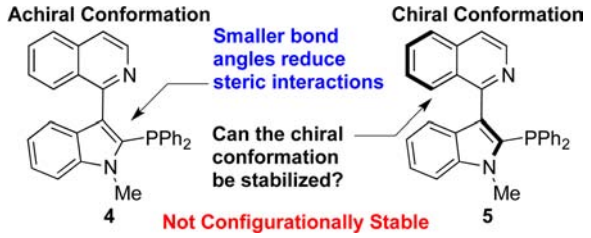


Figure 1. Configurationally unstable ligand **4**.

this may potentially be overcome by the incorporation of increasingly large *ortho*-substituents,[12] the central dogma for inducing atropisomerism, we hypothesized that a fundamental new approach to increasing the barrier to rotation could be developed to enable new classes of highly reactive and selective catalysts. More specifically, *we hypothesized that the barrier to rotation in biaryls can be increased by stabilizing the chiral ground-state conformation instead of destabilizing the planar transition state, leading to racemization* (Figure 1). Surprisingly, to the best of our knowledge, this strategy has never been explored. Herein we report our findings in this area including the design, synthesis, deracemization, and successful implementation of a chiral imidazole-based biaryl P,N-ligand for enantioselective copper acetylide addition.

The design of our ligand centers around the incorporation of a 5-membered electron-rich aromatic heterocycle that contains a coordinating atom and functional elements that stabilize the chiral conformation. At the outset we envisioned an imidazole-based system, providing a basic coordination site and a second nitrogen atom that could be appended with a group to stabilize the chiral conformation **7** through π-stacking interactions (Figure 2). This would provide a unique P,N-ligand with modified bite and dihedral angles.

The synthesis of racemic **7** was achieved in several straightforward steps starting with 2-hydroxy-1-naphthaldehyde **8**, whereby the requisite heterocycle and phosphino groups were readily introduced (Scheme 1). In the event, condensation of **8** with ammonium acetate and benzil furnished **9** in 80%

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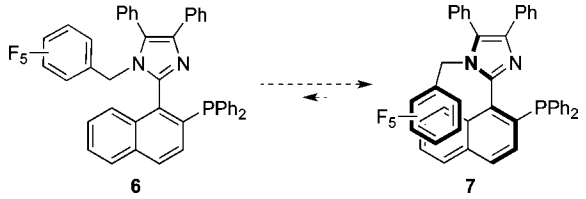
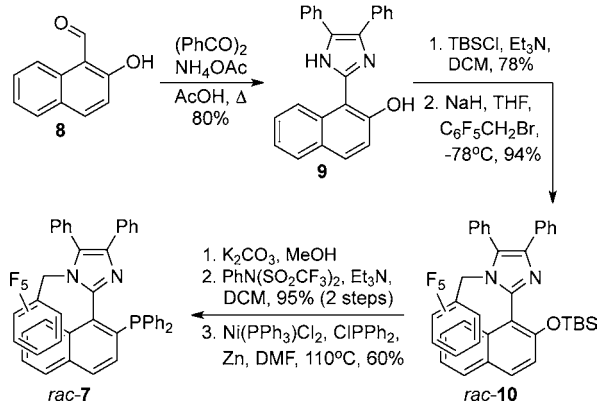


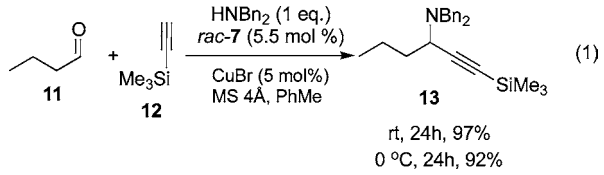
Figure 2. Stabilization of the chiral conformation in 7.

Scheme 1. Synthesis of Racemic Ligand 7



yield.[13] The free alcohol was then protected as the TBS ether, and the resulting imidazole was alkylated with pentafluorobenzyl bromide to yield **10**. The alcohol was then deprotected, converted to the triflate, and coupled[14] to produce *rac*-7 in ca. 33% overall yield from commercial materials. We were encouraged to find an AB pattern for the benzylic protons in the ^{1}H NMR spectrum of *rac*-7, indicating that they are diastereotopic on the NMR time scale.

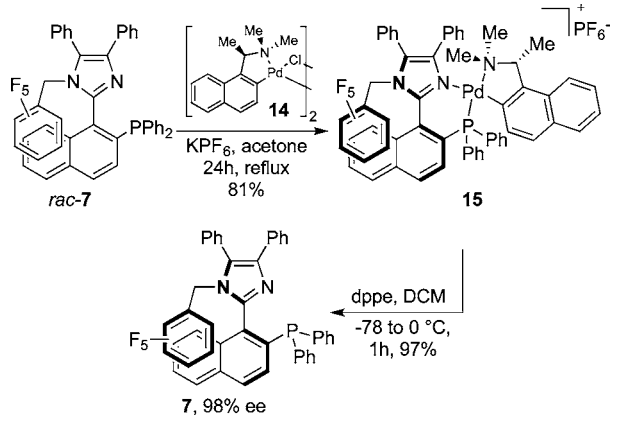
With a good source of 7 established, albeit racemic, it seemed prudent to perform a preliminary ligand acceleration effect study. To this end, *rac*-7 was employed in a copper-catalyzed A^3-coupling[15] of butyraldehyde, trimethylsilylacetylene, and dibenzylamine (eq 1). Much to our delight, amine product **13**



was isolated in 97% yield after 24 h at room temperature. Structurally, ligand 7 is significantly different than the known biaryl P,N-ligands such as QUINAP, where **13** is obtained in 88% after 120 h.[6,16] Extended reaction times of several days to a week are commonly observed using these ligands.[17] With *rac*-7, the reactivity was enhanced to such an extent that the reaction could even be performed at 0 °C, providing **13** in 92% yield after 24 h (eq 1). This should be advantageous for achieving high selectivities, and attempts were next made to obtain the ligand as a single enantiomer.

For QUINAP and derivatives containing only axial chirality, non-racemic material is typically obtained by resolution involving coordination to a chiral Pd salt, crystallization, and decomplexation.[5,11,18] Unfortunately, this strategy did not provide satisfactory results, and 7 could only be obtained in 85−90% ee. Fortunately, instead of resolving 7, after extensive optimization it was found that the racemic compound could be converted to a single enantiomer in a two-step process, in effect deracemizing it. To achieve this, *rac*-7 was treated with complex **14** and KPF_6 in refluxing acetone for 24 h to provide **15** in 81% yield as a single diastereomer whose structure was confirmed by X-ray crystallography (Scheme 2).[19,20] The free ligand was then obtained in high yield and 98% ee after treatment with dppe.[21]

Scheme 2. Deracemization of Ligand 7



Interestingly, the inclusion of KPF_6 is vital to the success of the reaction, as two non-interconverting diastereomers are observed in the absence of this additive. Control experiments were performed to study this issue, and an equal mixture of two diastereomers was formed when KPF_6 was omitted but under otherwise identical reaction conditions. Additionally, re-complexation of 7 (98% ee) to **14** results in a single diastereomer that does not revert to the same 1:1 mixture of diastereomers upon heating.

It is important to note that 7 is configurationally stable, and samples of the ligand have been stored for several months with no loss of optical purity. One further question regarding the structure involves the role of the C_6F_5 group and π-stacking. Evidence of π-stacking was obtained early on when X-ray-quality single crystals were grown from a sample of *rac*-7 and the structure was solved (Figure 3).[19] The F_5-phenyl group is

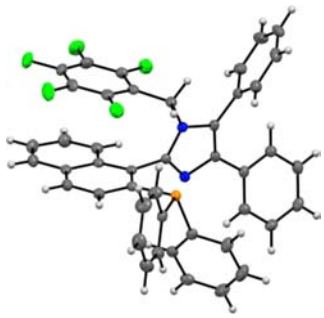


Figure 3. X-ray crystal structure showing π-stacking.

π-stacking with the naphthalene ring at a mean distance of 3.36 Å in a parallel, offset stack.[22] This demonstrates that π-stacking is possible in the solid state, but does not necessarily indicate that it has any influence on the barrier to rotation in solution. Literature protocols used to study π-stacking involve modification of the substitution on one of the aromatic rings.[22] To probe this issue, a comparison of barrier heights between 7 and a compound that would maintain the steric

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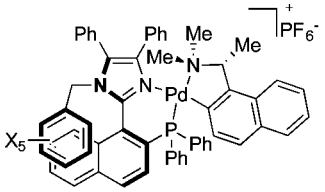
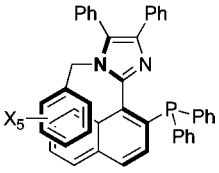
profile but perturb the ability to π-stack was needed. In accord with literature precedent, the corresponding non-fluorinated compound was chosen because if the effect was purely steric, no significant difference would be expected. If π-stacking is indeed involved in the solution phase, a significant difference in barrier height should be observed.

To make the necessary comparisons, 7-$\mathbf{H_5}$ was prepared from **8** using the route outlined above.[19] Interestingly, the penultimate non-flourinated palladium complex **15**-$\mathbf{H_5}$ was configurationally unstable, and the 1:1 diastereomeric mixture of complexes prepared from racemic 7-$\mathbf{H_5}$ converged on a single diastereomer upon standing at room temperature for 24 h. When 7-$\mathbf{H_5}$ was liberated from the Pd complex, it was obtained in 52% ee, in stark contrast to **7** which was isolated in 98% ee. Racemization studies were performed[23] on both 7-$\mathbf{H_5}$ and **7** to obtain their barriers to rotation, and it was found that 7-$\mathbf{H_5}$ has a half-life of 22 min at 75 °C in DCE, whereas **7** has a half-life of 8.70 h.[19] This corresponds to $\Delta\Delta G^{\ddagger}_{75^\circ C}$ = 2.2 kcal/mol,[19] a value that is within the range of previously reported values for π-stacking,[22] and demonstrates that the electronic perturbation by simple inclusion of the fluorine atoms significantly increases the barrier to rotation.



15, X = F
15-$\mathbf{H_5}$, X = H

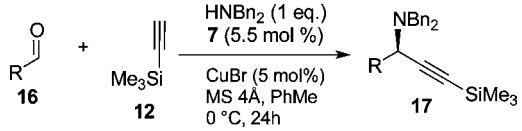


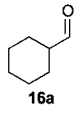
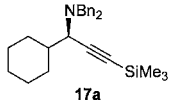
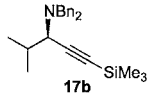
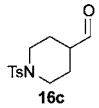
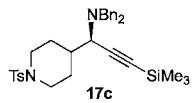
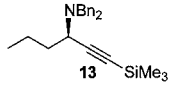
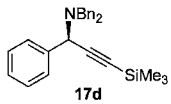
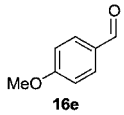
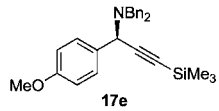
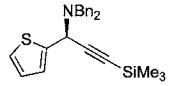
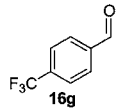
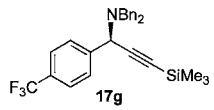
7, X = F (98% ee)
7-$\mathbf{H_5}$, X = H (52% ee)

With the new chiral non-racemic ligand **7** in hand, we turned our attention to testing its performance in an enantioselective transformation. To this end, **7** was employed in the enantioselective A^3-coupling. As can be seen in Table 1, the reactions were highly enantioselective over a range of aldehydes. As might be expected,[15] with aliphatic aldehydes α-substitution increases selectivity (e.g., entry 1 vs 4). It is also noteworthy that, using **7**, these conditions work well for aromatic aldehydes, which are the most challenging substrates for the reaction.[17] Remarkably, the presence of electron-donating or -withdrawing groups has little effect on selectivity (entries 5–9), nor does the reaction temperature. When **16g** was allowed to react at 0 °C, the reaction was very slow, yielding **17g** in only 15% after 4 days, but in 95% ee (entry 8). Increasing the temperature to 22 °C restored the reactivity to an acceptable level (70% yield after 24 h) and had little effect on the ee (entry 9). In comparison, the previous best yield obtained with this electron-deficient aldehyde was 43% after 4 days to obtain the product in 63% ee.[17a]

Carreira has also developed modified conditions to employ the amine **19**, which is readily deprotected.[24] With these conditions, using the PINAP ligand, they report that aromatic aldehydes do not provide satisfactory results.[24] In contrast, ligand **7** enables the use of both aliphatic and aromatic aldehydes with high enantioselectivity (Scheme 3). These results lead to the conclusion that **7** is the best ligand for the enantioselective A^3-coupling to date, displaying the highest levels of reactivity and selectivity over the broadest range of substrates. More importantly, these results demonstrate the potential of the new design element exemplified by **7**.

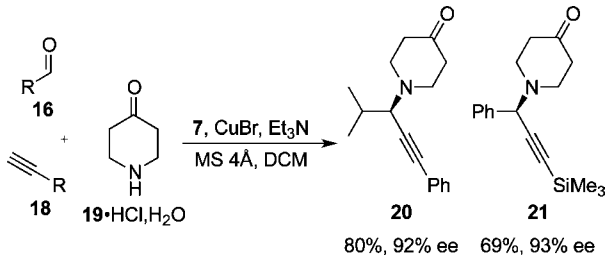
Table 1. Enantioselective A^3-Coupling Employing 7[a]



entry	aldehyde	product	yield (%)[b]	ee (%)
1	 **16a**	 **17a**	95	97[c]
2	 **16b**	 **17b**	92	95[c]
3	 **16c**	 **17c**	94	91
4	 **11**	 **13**	92	89[c]
5	 **16d**	 **17d**	80	94[c]
6	 **16e**	 **17e**	77	94[d]
7	 **16f**	 **17f**	60	94[c,d]
8	 **16g**	 **17g**	15	95[c,d]
9			70	92[c,e]

[a]See Supporting Information for full experimental details. [b]Isolated yields of purified compounds. [c]Determined after desilyation. [d]Reaction allowed to run for 4 days at 0 °C. [e]Reaction allowed to run for 24 h at 22 °C.

Scheme 3. Alkyne Addition with 19



In summary, we have developed a new concept for increasing the barrier to rotation in biaryls whereby the chiral ground-state conformation is stabilized by π-stacking interactions. This strategy was successfully applied to the design of ligand **7**, a

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new chiral biaryl P,N-ligand incorporating a 5-membered electron-rich heteroaromatic. The ligand is straightforward to prepare and has been demonstrated to be a superb catalyst for the enantioselective A^3-coupling reaction. More importantly, this design concept should be broadly applicable and enable a new class of 5-membered heteroaromatic biaryls to be prepared as catalysts for a range of reactions. Further studies on this are underway in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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