ORGANIC LETTERS

2008
Vol. 10, No. 4
545−548

Click-Connected Ligand Scaffolds: Macrocyclic Chelates for Asymmetric Hydrogenation

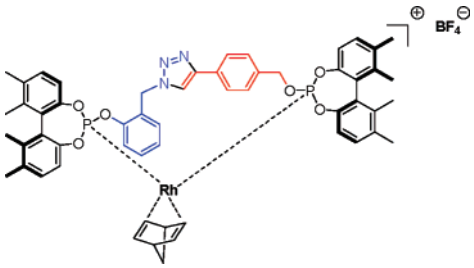
Qing Zhang and James M. Takacs*

Department of Chemistry, University of Nebraska−Lincoln, Lincoln, Nebraska 68588-0304

jtakacs1@unl.edu

Received November 30, 2007

ABSTRACT



Click chemistry is used to construct ligand scaffolds for a series of chiral diphosphites. Enantioselectivity as high as 97% ee is obtained using these click ligands in rhodium-catalyzed asymmetric hydrogenation. Control experiments and spectroscopic data suggest that a 16-membered *P,P*-macrocyclic Rh(I) chelate is formed.

The goal of all chiral ligand designs is to (i) create a chiral "catalytic pocket" (topography) around the metal to direct stereochemistry and (ii) impart the appropriate electronic characteristics at that metal center for efficient catalysis. Most modular ligand designs start with one or a small set of "interesting scaffolds" and sequentially append the ligating groups.[1] The challenge is to find the "correct ligating group", one appropriately oriented by the selected scaffold to form an efficient catalyst.

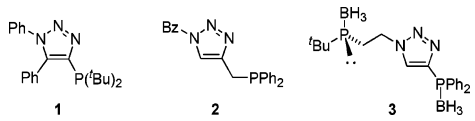
Ligand scaffold optimization is an alternative design strategy for improving catalyst efficiency.[2] It relies upon the ability to generate a collection of ligand scaffolds that define a diverse set of topographies or chiral space to be explored. The overall strategy is simple; use the nature of the ligating group to define the electronic nature of the metal−ligand interaction and a chiral surface, and then the ligand scaffold is varied to find an optimal orientation of that surface for asymmetric catalysis. Put to practice, the ligand scaffold is constructed by connecting subunits, each typically a unique structure and ligating group, via a facile chemical reaction or suitable intermolecular association.[3] Combining different subunits creates a diverse set of scaffolds and ligating groups.

The alkyne−azide [3+2]-cycloaddition reaction, i.e., "click chemistry",[4] has been applied to a wide range of problems for which the advantages of a fast, clean coupling reaction can be exploited;[5] several applications to the preparation of novel ligands are among them.[6] For example, the preparation and use of chelating *P,N*-ligands was recently described by Zhang[7] (e.g., **1**) and Reek[8] (e.g., **2**). Kann and co-workers[9] recently reported the use of click chemistry for the preparation of a library of *P*-chirogenic ligands, including a diphosphine derivative, **3**.

(1) (a) Gennari, C.; Piarulli, U. *Chem. Rev.* **2003**, *103*, 3071−3100.
(2) (a) Moteki, S. A.; Takacs, J. M. *Angew. Chem., Int. Ed.* **2007**, *46*, in press. (b) Takacs, J. M.; Chaiseeda, K.; Moteki, S. A.; Reddy, D. S.; Wu, D.; Chandra, K. *Pure Appl. Chem.* **2006**, *78*, 501−509. (c) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494−4495.

(3) (a) Sandee, A. J.; Reek, J. N. H. *Dalton Trans.* **2006**, 3385−3391. (b) Reyes, S. J.; Burgess, K. *Chem. Soc. Rev.* **2006**, *35*, 416−423. (c) Wilkinson, M. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Org. Biomol. Chem.* **2005**, *3*, 2371−2383. (d) Breit, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 6816−6825.
(4) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.
(5) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249−1262.

10.1021/ol702890s CCC: $40.75
Published on Web 01/12/2008



Our application of click chemistry to ligand scaffold construction is shown in Figure 1. The 2-, 3-, and 4-hydroxy-

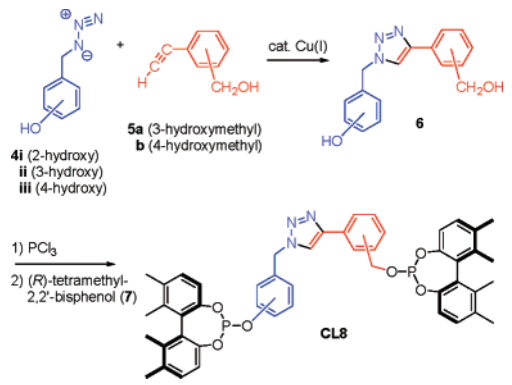
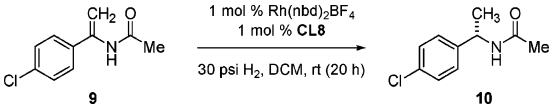


Figure 1. Facile, modular route to novel ligand scaffolds via click chemistry.

phenyl azides **4i**−**iii** are coupled with the 3- and 4-(hydroxymethyl)phenyl acetylenes (**5a**,**b**) to afford the six isomeric diols represented by structure **6**. Coupling each of the diols with phosphorus trichloride and (*R*)-tetramethyl-2,2′-bisphenol[10] (**7**) affords a set of isomeric click ligands **CL8**. These chiral diphosphites differ only with respect to the structure of the ligand scaffold.

Asymmetric hydrogenation is a common testing ground for evaluating new ligand designs,[11] and the six diphosphites were used in conjunction with $Rh(nbd)_2(BF_4)$ to effect the hydrogenation of enamide **9** (Table 1).[12] The reactions were

Table 1. Screening Click Ligands in the Rhodium-Catalyzed Asymmetric Hydrogenation of Enamide **9**



entry	CL8	% yield	% ee
1	**8ia**	99	88
2	**8ib**	99	96
3	**8iia**	97	95
4	**8iib**	83	89
5	**8iiia**	30	91
6	**8iiib**	52	85

run under a standard set of reaction conditions (30 psi H_2, DCM, rt, 20 h). Each click ligand affords the secondary amine derivative (*S*)-**10** with enantiomeric excesses ranging from 85% (entry 6, **CL8iiib**) to 96% (entry 2, **CL8ib**). In addition to the variation in enantiomeric excess, we find the degree of conversion obtained under these standard reaction conditions varies as a function of the ligand scaffold. The chemical yield of (*S*)-**10** varies from 30% (entry 5, **CL8iiia**) to near-quantitative (entries 1 and 2, **CL8ia** and **CL8ib**). Click ligands **CL8ib** (99%, 96% ee) and **CL8iia** (97% yield, 95% ee) give the overall most promising results.

There are four potential ligating sites in **CL8ib** (Figure 2) raising questions as to whether it functions as a *P*,*N*- or

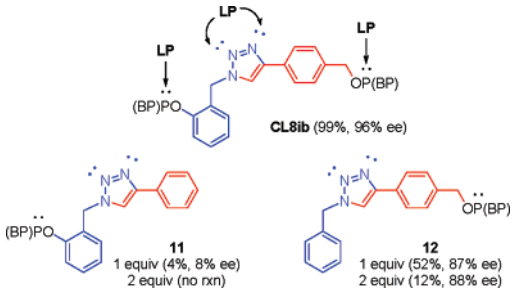


Figure 2. Diminished reactivity and enantioselectivity with triazole monophosphites **11** and **12** suggests that both phosphite moieties in **CL8ib** are involved in the active catalyst.

P,*P*-ligand, or perhaps a tri- or tetradentate ligand,[13] if it indeed chelates at all. If *P*,*N*-chelation is important, then it seems likely that either or both of the truncated triazole monophosphites **11** and **12** would give results comparable to those obtained with **CL8ib**. Neither does. Two ligand to metal ratios were examined for **11** and **12** in the hydrogenation of **9**. **11** affords a poor catalyst at either a 1:1 or 2:1 ratio. **12** exhibits poor reactivity at the 2:1 **12**/Rh(I) ratio. The reactivity is improved at the 1:1 ratio, suggesting that *P*,*N*-ligation may be relevant for **12**, although it is not clear how its structure can accommodate *P*,*N*-chelation within the

(6) (a) Suijkerbuijk, B. M. J. M.; Aerts, B. N. H.; Dijkstra, H. P.; Lutz, M.; Spek, A. L.; van Koten, G.; Klein Gebbink, R. J. M. *Dalton Trans.* **2007**, 1273−1276. (b) Bastero, A.; Font, D.; Pericas, M. A. *J. Org. Chem.* **2007**, *72*, 2460−2468. (c) Mindt, T. L.; Struthers, H.; Brans, L.; Anguelov, T.; Schweinsberg, C.; Maes, V.; Tourwe, D.; Schibli, R. *J. Am. Chem. Soc.* **2006**, *128*, 15096−15097. (d) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853−2855.

(7) (a) Liu, D.; Gao, W.; Dai, Q.; Zhang, X. *Org. Lett.* **2005**, *7*, 4907−4910. (b) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928−3934. (c) See also: Fukuzawa, S.-i.; Oki, H.; Hosaka, M.; Sugasawa, J.; Kikuchi, S. *Org. Lett.* **2007**, *9*, 5557−5560.

(8) Detz, R. J.; Arevalo Heras, S.; De Gelder, R.; Van Leeuwen, P. W. N. M.; Hiemstra, H.; Reek, J. N. H.; Van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 3227−3230.

(9) Dolhem, F.; Johansson, M. J.; Antonsson, T.; Kann, N. *J. Comb. Chem.* **2007**, *9*, 477−486.

(10) (a) Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831−3834. (b) Rubio, M.; Suarez, A.; Alvarez, E.; Pizzano, A. *Chem. Commun.* **2005**, 628−630. (c) Rubio, M.; Vargas, S.; Suarez, A.; Alvarez, E.; Pizzano, A. *Chem. Eur. J.* **2007**, *13*, 1821−1833.

(11) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103−151.

(12) For recent examples of the use of diphosphites in rhodium-catalyzed asymmetric hydrogenation, see: (a) Reetz, M. T.; Mehler, G.; Bondarev, O. *Chem. Commun.* **2006**, 2292−2294. (b) Junge, K.; Hagemann, B.; Enthaler, S.; Erre, G.; Beller, M. *ARKIVOC* **2007**, 50−66. (c) Axet, M. R.; Benet-Buchholz, J.; Claver, C.; Castillon, S. *Adv. Synth. Catal.* **2007**, *349*, 1983−1998. (d) Marson, A.; Freixa, Z.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **2007**, 4587−4591.

constraints of a 1:1 complex. Nevertheless, even using the better ratio, the yield and enantioselectivity are still lower than that observed using **CL8ib**. These results suggest that *P*,*P*-chelation is the important mode for **CL8ib**; that is, both phosphite moieties are involved in the active catalyst.[14]

It is tempting to assume that the active catalyst is a 1:1 **CL8ib**:Rh(I) complex, rather than 2:2 or some higher multiple complex or an ensemble of oligomers. While many macrocyclic metal−ligand chelates have been characterized and others invoked to explain efficient asymmetric catalysis,[15] the 1:1 complex with **CL8ib** requires a 16-membered *P*,*P*-macrocyclic chelate that preliminary modeling studies indicate should be quite strained.[16] Nonetheless, other data are consistent with its formation.

The first piece of evidence derives from the work of Kagan on nonlinear effects in asymmetric catalysis.[17] As outlined in Figure 3, if the active catalyst is the 1:1 complex, a mixture

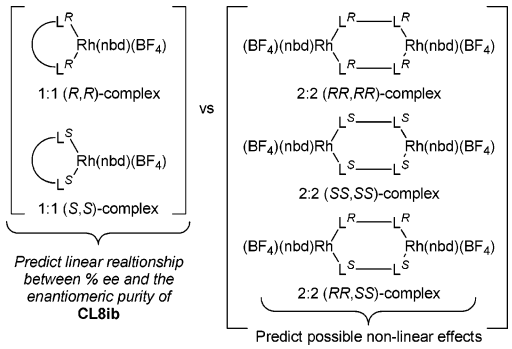


Figure 3. Predicted consequences of 1:1 or 2:2 ligand/metal complexation of **CL8ib** with Rh(nbd)(BF_4).

of enantiomer ligands will give a mixture of enantiomeric 1:1 complexes or, equivalently, a mixture of enantiomeric catalysts. Thus, a linear relationship between the observed enantioselectivity of the catalyzed reaction and the enantiomeric purity of the click ligand used is expected; nonlinear effects are precluded. However, if the 2:2 complex (or some higher homologue or an oligomeric mixture) competes, then at least three species are expected to contribute, the enantiomeric *all-R* and *all-S* complexes and the diastereomeric *R*/*S*-mixed complex. If, as is often the case, the *R*/*S*-mixed complex forms preferentially or the diastereomeric catalysts exhibit significantly different rates, then nonlinear effects are expected.

The rhodium-catalyzed hydrogenation of enamide **9** was carried out using various ratios of the enantiomers of **CL8ib**. As shown in Figure 4, we find a linear relation between the

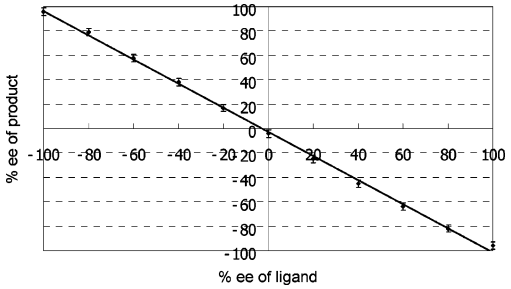


Figure 4. Linear relation between the enantiomeric purity of **CL8ib** and the enantioselectivity observed in the rhodium-catalyzed asymmetric hydrogenation of enamide **9**.

enantiomeric purity of the click ligand and the enantioselectivity of the hydrogenation. This result, while not unambiguous proof, is consistent with the 1:1 16-membered *P*,*P*-macrocyclic Rh(I) chelate being relevant to the efficient asymmetric catalysis observed.

The ^{31}P NMR spectrum of the free click ligand **CL8ib** shows singlets at 130.6 and 135.3 ppm. As shown in Figure 5, the (**CL8ib**)Rh(nbd)(BF_4) complex shows two sets of resonances, 127.0 and 148.1 ppm, in a 1:1 ratio; each is a doublet of doublets. The coupling constants $J_{Rh,P(1)} = 221$ Hz, $J_{Rh,P(2)} = 234$ Hz, and $J_{P(1),P(2)} = 77$ Hz are consistent with the chelated structure shown. The mass spectrum shows a peak corresponding to the complex minus BF_4; its isotopic distribution pattern is in good agreement with theory. High-resolution mass spectrometry (FAB, 3-NBA matrix) determines the exact mass as *m*/*z* 1016.2417, a value in close agreement with the 1016.2465 theoretical value for $C_{55}H_{53}N_3O_6P_2Rh$ (M − BF_4).

The phosphite moieties in **CL8ib** differ slightly, one a benzyl phosphite, the other a phenyl phosphite. Several related structures were prepared and evaluated (Figure 6). For example, a derivative in which a methyl substituent is present at the benzylic position was prepared. This added methyl substituent makes the ligand scaffold chiral; the *R*- and *S*-scaffolds afford the diastereomeric diphosphites **CL13** and **CL14**, respectively. The former click ligand shows somewhat diminished enantioselectivity while the latter gives results comparable to those obtained with the parent ligand **CL8ib**.

Substituting a phenyl for the benzyl phosphite moiety markedly diminishes the efficiency of the ligand. **CL15** exhibits low turnover (7% yield, 72% ee). In contrast, replacing the phenyl phosphite with a second benzyl phosphite (i.e., **CL16**) has relatively little effect (99% yield, 92% ee).

Slightly improved results are found with **CL17** (99% yield, 97% ee). This diphosphite is isomeric with **CL8ib** and is

(13) Tetradentate coordination to Rh(I) seems unlikely on the basis of structural constraints and the fact that these ligands function efficiently in asymmetric hydrogenation, a reaction in which tetradentate coordination is unsuitable. See: Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746−1754.

(14) For **CL8ib**, the catalytic activity drops off substantially at higher ligand to Rh(I) ratios.

(15) (a) Hattori, G.; Hori, T.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12930−12931. (b) Birkholz, M.-N.; Dubrovina, N. V.; Jiao, H.; Michalik, D.; Holz, J.; Paciello, R.; Breit, B.; Boerner, A. *Chem. Eur. J.* **2007**, *13*, 5896−5907. (c) Wassenaar, J.; Reek, J. N. H. *Dalton Trans.* **2007**, 3750−3753. (d) Jiang, X.-B.; Lefort, L.; Goudriaan, P. E.; de Vries, A. H. M.; van Leeuwen, P. W. N. M.; de Vries, J. G.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1223−1227. (e) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *J. Am. Chem. Soc.* **2006**, *128*, 4188−4189.

(16) We thank the reviewer for bringing this to our attention.

(17) Kagan, H. B. *Synlett* **2001**, 888−899.

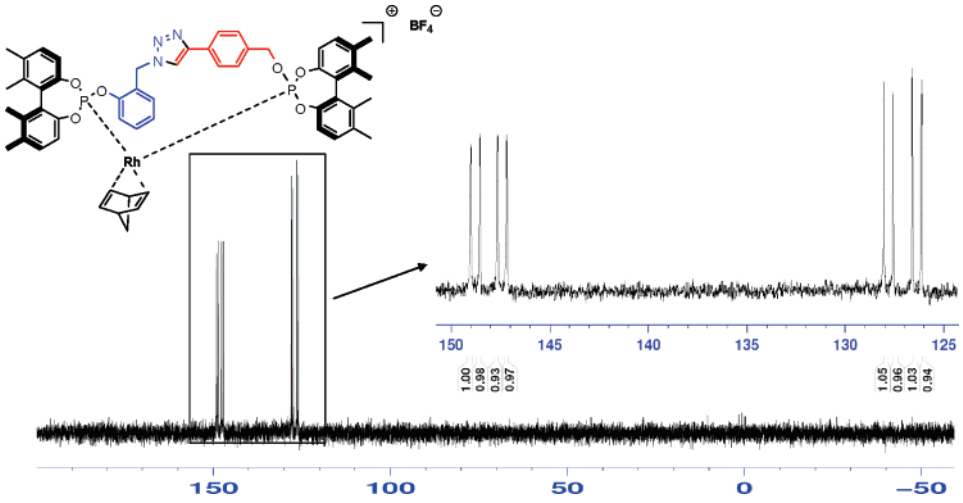


Figure 5. ^{31}P NMR spectrum of (**CL8ib**)Rh(nbd)(BF_4): $J_{Rh,P(1)}$ = 221 Hz, $J_{Rh,P(2)}$ = 234 Hz, and $J_{P(1),P(2)}$ = 77 Hz.

prepared by swapping the alkyne and azide subunits; that is, the alkyne precursor incorporates the *p*-benzyl alcohol subunit and the azide subunit incorporates the *o*-phenol subunit. Click ligand **CL17** was used in a larger scale hydrogenation of enamide **9** at a lower catalyst load (1 mmole of **9**, 0.1 mol % catalyst) but no attempt to otherwise further optimize the reaction conditions (DCM, 30 psi H_2, 10 h, rt). Under these conditions, **CL17** gives 92% yield of (*S*)-**10** with 96% ee. Click ligand **CL17** is also effective with several other common test substrates. Each of the substrates in Figure 7 gives 90% ee or greater (0.5 mmol substrate, 0.2 mol % catalyst, DCM, 30 psi H_2, 16−20 h, rt).

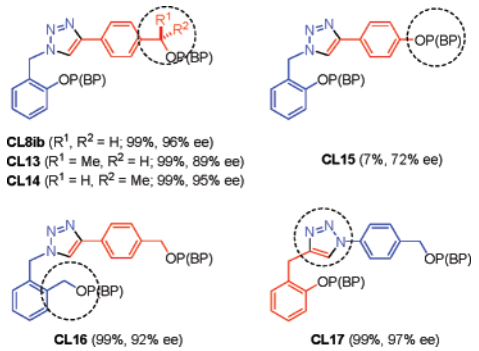


Figure 6. Fine-tuning the click ligand scaffold structure.

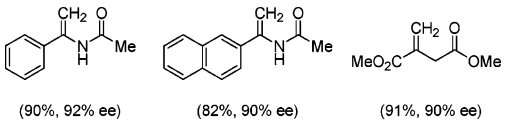


Figure 7. Efficient (**CL17**)Rh(nbd)(BF_4)-catalyzed asymmetric hydrogenation of related substrates.

In summary, click chemistry lends itself to the ligand scaffold optimization approach to chiral catalyst discovery and development. The facile alkyne−azide [3 + 2]-cycloaddition reaction was used to prepare a small library of chiral triazole diphosphites. While these novel chiral ligands differ only in the scaffold structure, their performance with respect to yield and asymmetric induction varies significantly in a common test case for asymmetric catalysts, rhodium-catalyzed asymmetric hydrogenation. Enantioselectivity as high as 97% ee is achieved. ^{31}P NMR and mass spectral analyses, as well as the results obtained using truncated monophosphites and the lack of a nonlinear effect, suggest an important role for a 16-membered *P*,*P*-macrocyclic (**CL8ib**)Rh(I) complex in the reaction, although preliminary modeling studies find this proposed complex to be quite strained. The related **CL8iia** complex is less strained and exhibits similar reactivity. Further studies into the nature of these complexes and their role in catalysis are in progress.

Acknowledgment. Financial support for this research under grants from the Nebraska Research Initiative, ACS-PRF (47257-AC1), and NSF (CHE-0316825) is gratefully acknowledged. We thank T. A. George (UNL Chemistry) for the loan of equipment, S. Smith (UNL Chemistry) for preparing tetramethyl-2,2′-bisphenol, and the NSF (CHE-0091975, MRI-0079750) and NIH (SIG-1-510-RR-06307) for the NMR spectrometers used in these studies carried out in facilities renovated under NIH RR016544.

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

OL702890S