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Enantioselective Cu-Catalyzed Conjugate Addition of Diethylzinc to Acyclic Aliphatic Enones

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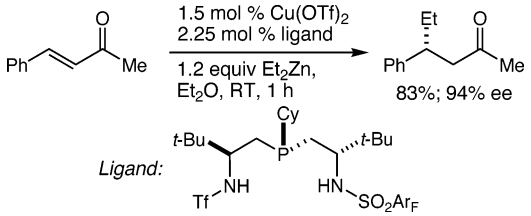
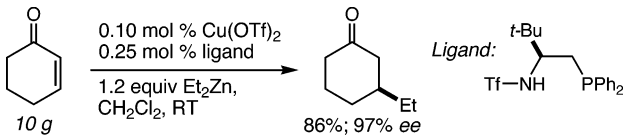
ABSTRACT



A new P-chiral phosphine bis(sulfonamide) ligand has been developed that allows the Cu-catalyzed enantioselective conjugate addition of Et_2Zn to acyclic aliphatic enones. The reactions proceed with excellent levels of enantioselectivity (90–95% ee) with a range of enone substrates, involve the use of only 1.2 equiv of Et_2Zn, and give best results at ambient temperature.

The asymmetric copper-catalyzed addition of dialkylzinc reagents to enones has matured into a powerful carbon−carbon bond forming method,[1] as a variety of highly enantioselective (>90% ee) ligands/methods for cyclic enones[2] and for benzylideneacetones and chalcones[2b,3] have been reported. Aliphatic acyclic enones have proven to be a far more challenging substrate class, however. Although some substrate-specific successes have been recorded,[4] to date there has been only one report of a highly enantioselective and general catalyst for this substrate class.[5] We recently reported a highly practical method for the addition of dialkylzinc reagents to cyclic enones that employs a simple phosphine sulfonamide ligand (Scheme 1).[6] Subsequent studies have shown that this ligand performs poorly with acyclic enones. Given the appeal of the reaction described in Scheme 1, we wondered whether this ligand could be modified to address this limitation and report herein the development of a ligand that is highly enantioselective and general for a range of aliphatic acyclic enones.

Scheme 1



Our investigations began with the hypothesis that the addition of a third donor element to the ligand scaffold might lead to an improved catalyst. One straightforward way to

(1) For recent reviews, see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353.

(2) See ref 1 and (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263. (c) Liang, L.; Au−Yeung, T. T.-L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799−3801. (d) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363.

(3) (a) Hu, X.; Chen, H.; Zhang, X. *Angew.* Chem., Int. Ed. **1999**, *38*, 3518−3521. (b) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699−3702. (c) Hu, Y.; Liang, X.; Wang, J.; Zheng, Z.; Hu, X. *Tetrahedron: Asymmetry* **2003**, *14*, 3907−3915. (d) Morimoto, T.; Mochizuki, N.; Suzuki, M. *Tetrahedron Lett.* **2004**, *45*, 5717−5722.

(4) (a) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375−1378. (b) Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660−5667.

(5) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781.

(6) Krauss, I. J.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3201−3203.

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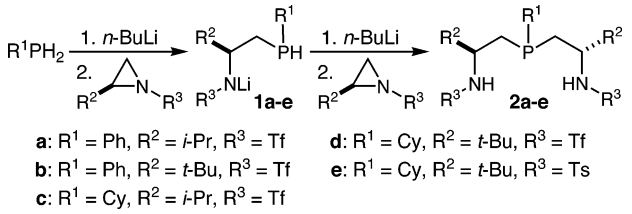
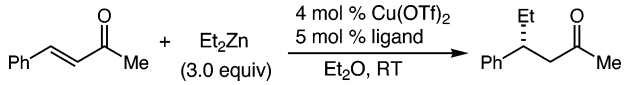
Scheme 2



accomplish this would be the introduction of a second sulfonamide, affording (potentially) tridentate phosphine bis(sulfonamide) ([NPN]) ligands.[7] The synthesis of several phosphine bis(sulfonamides) followed the iterative one-pot procedure shown in Scheme 2. A primary phosphine was deprotonated using *n*-BuLi, and the resulting lithium phosphide was treated with 1 equiv of an aziridine[8] to give the lithiated phosphine sulfonamide intermediate (**1a**−**e**). This sequence was then repeated to append the second sulfonamide arm. Phosphine bis(sulfonamides) **2a**−**e** were prepared in this fashion and isolated as moderately air-sensitive colorless oils or white solids.

With these new ligands **2a**−**e** in hand, an initial screen of their performance in the $Cu(OTf)_2$-catalyzed conjugate addition of Et_2Zn to benzylidene acetone was performed (Table 1). All reactions were carried out in Et_2O at ambient

Table 1. Performance of Ligands **2a**−**e**

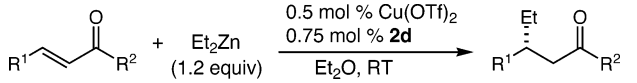


entry	ligand	R^1	R^2	R^3	ee[a]
1	**2a**	Ph	*i*-Pr	Tf	48
2	**2b**	Ph	*t*-Bu	Tf	12
3	**2c**	Cy	*i*-Pr	Tf	79
4	**2d**	Cy	*t*-Bu	Tf	84
5	**2e**	Cy	*t*-Bu	Ts	67

[a] Enantiomeric excess determined by chiral GC (CDGTA).

temperature as these proved to be optimal conditions. Reactions with phenylphosphine-derived ligands **2a** and **2b** were sluggish and afforded the conjugate addition product in poor to modest enantioselectivities (entries 1 and 2). In contrast, the more basic cyclohexylphosphine-derived ligand **2c** yielded a substantial improvement in enantioselectivity (entry 3). A further substitution of *tert*-butyl for *iso*-propyl on the ligand backbone (**2d**) resulted in an increase in selectivity to 84% ee (entry 4). Finally, bis(tosylamide) **2e** performed significantly less well (entry 5), establishing the superior performance of the triflamide group.

Table 2. Scope of Reaction with Ligand **2d**



entry	R^1	R^2	yield (%)	ee[a]
1	Ph	Me	67	87
2	Me	*n*-Hex	71	88
3	*n*-Pent	Me	69	84
4	*i*-Pr	Me	79	85

[a] Enantiomeric excess determined by chiral GC (CDGTA).

On the basis of these initial studies, ligand **2d** was selected for further study. Of particular interest was whether **2d** would provide consistent levels of enantioselectivity for conjugate additions to a range of acyclic aliphatic enones (Table 2). Further optimization revealed that the catalyst loading and the amount of Et_2Zn could be significantly reduced. As shown, under these optimized conditions ligand **2d** consistently provided enantioselectivities in the 84−88% ee range for several aliphatic enones (entries 1−4).

Although phosphine bis(sulfonamides) are potentially tridentate ligands, it is unlikely that the species responsible for catalysis would have all three donors of the [NPN] ligand and the requisite alkyl residue bound to a single Cu center; such a coordinatively and electronically saturated complex would not be expected to be reactive. More likely is that one of the sulfonamides is not associated with the Cu during catalysis but rather performs a distinct function. We therefore considered ligands bearing two different sulfonamide groups, with the expectation that each of the sulfonamides could be tuned to optimize its specific reaction role.

Treatment of lithium cyclohexylphosphide with the aziridine derived from (*S*)-*tert*-leucinol and Tf_2O gave phosphine sulfonamide **3** as a mixture (1.3:1) of diastereomers in 88% yield (Scheme 3). The second sulfonamide arm of the ligand was installed under neutral conditions by reaction of **3** with the aziridine derived from (*S*)-*tert*-leucinol and 3,5-bis(trifluoromethyl)bezenesulfonyl chloride (Ar_FSO_2Cl) in CF_3CH_2OH at 70 °C. After treatment with $BH_3{\cdot}Me_2S$, the diastereomeric phosphine−borane complexes **4a** and **4b** (dr = 1.5:1.0) were separated and isolated as air-stable solids (79% total yield).[9] Deprotection of **4a** and **4b** with 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded *P*-chiral [NPN′] ligands **5a** and **5b** in 84% and 76% yield, respectively.[10]

The performance of ligands **5a** and **5b** was then compared in the $Cu(OTf)_2$-catalyzed addition of Et_2Zn to benzylidene acetone (Scheme 4). In terms of enantioselectivity, ligand

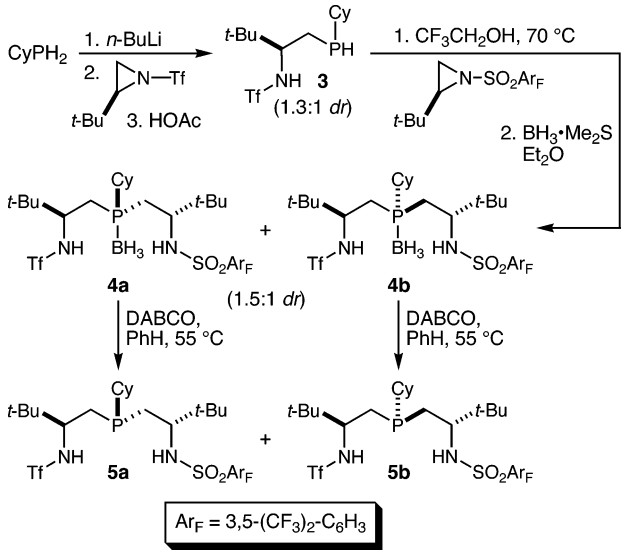
(7) This is a new ligand class. For related [NPN] ligands, see: (a) Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 6565−6568. (b) Schrock, R. R.; Seidel, S. W.; Schrodi, Y.; Davis, W. M. *Organometallics* **1999**, *18*, 428−437. (c) Fryzuk, M. D.; Johnson, S. A.; Rettig, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 11024−11025.

(8) Cernerud, M.; Skrinning, A.; Bérgère, I.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, *8*, 3437−3441.

(9) An X-ray crystallographic study of the minor diastereomer allowed the assignment of relative configuration for **4a** and **4b**. See Supporting Information.

(10) During the course of this work, Nelson reported the synthesis of an amino bis(sulfonamide) ligand bearing identical differential substitution on the two sulfonamide arms: Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14−15.

Scheme 3



5a proved superior to ligand **5b**, and both provided improvement over ligand **2d**. A significant difference in the efficiency of the catalysis with ligands **5a** and **5b** was noted as well. Prior to settling on **5a** as the ligand of choice, it seemed prudent to examine the performance of the pseudosymmetric bis(Ar_F) sulfonamide ligand **6**. As shown, although **6** provided excellent enantioselectivity, the efficiency of catalysis was inferior and similar to that of ligand **5b**. Taken together, these results provide compelling evidence for different roles for the two sulfonamide groups in the catalytic cycle (an example of bifunctional catalysis), one likely associated with the copper center during catalysis and the other likely performing a distinct function that can be independently optimized.

Ligand **5a** was evaluated with several different aliphatic acyclic enones (Table 3). Optimized conditions involved the use of only 1.2 equiv of Et_2Zn, 1.5 mol % of $Cu(OTf)_2$, and 2.25 mol % of ligand **5a**. Under these conditions, consistently

Scheme 4

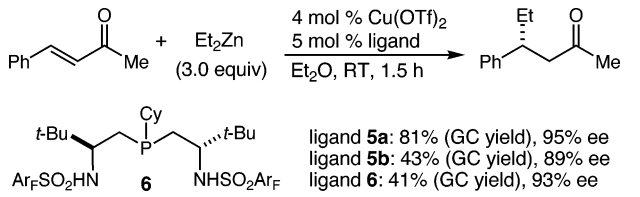
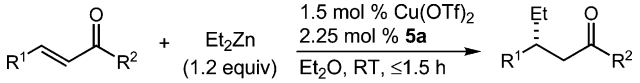


Table 3. Scope of Reaction with Ligand **5a**



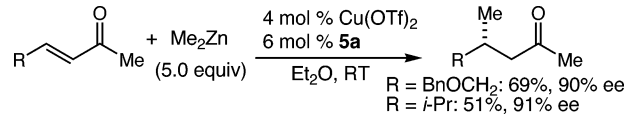
entry	R^1	R^2	yield (%)	ee[a]
1	Ph	Me	83	94
2	Me	*n*-Hex	76	95
3	*n*-Pent	Me	81	90
4	*i*-Pr	Me	76	91
5	$BnOCH_2$	Me	73	90

[a] Enantiomeric excess determined by chiral GC (CDGTA).

excellent enantioselectivities were obtained with a range of aliphatic acyclic enones (90−95% ee, entries 1−5).

The performance of ligand **5a** with dimethylzinc was also probed (Scheme 5). Although these reactions were less

Scheme 5



efficient and required somewhat higher catalyst loadings, excellent enantioselectivities were nevertheless observed.

We have reported the development of a new *P*-chiral [NPN′] phosphine bis(sulfonamide) ligand that provides excellent levels of enantioselectivity in the Cu-catalyzed conjugate addition of Et_2Zn to acyclic aliphatic enones. The reactions are practical, requiring only 1.2 equiv of Et_2Zn and proceeding in less than 1.5 h in Et_2O at ambient temperature. In addition, we have provided evidence that the two sulfonamides play distinct roles in the reaction. Further development of this new ligand class may be anticipated, and such studies are in progress.

Acknowledgment. We thank Dr. Kevin Janak (Parkin research group) for the X-ray structure of **4b**. The NIH (NIGMS) is gratefully acknowledged for a postdoctoral fellowship to A.P.D. We are grateful to Amgen for generous research support.

Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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