ORGANIC LETTERS
2003
Vol. 5, No. 18
3201−3203

Highly Practical and Enantioselective Cu-Catalyzed Conjugate Addition of Alkylzinc Reagents to Cyclic Enones at Ambient Temperature

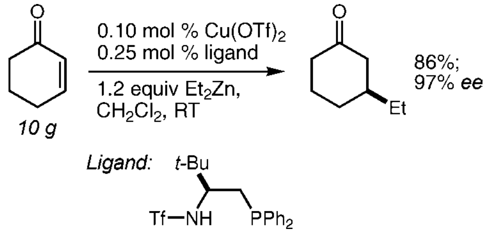
Isaac J. Krauss and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027

leighton@chem.columbia.edu

Received June 2, 2003

ABSTRACT



A new ligand for Cu-catalyzed enantioselective additions of dialkylzincs to cyclic enones has been developed. In addition to providing good to excellent enantioselectivities with a range of cyclic enones and dialkylzincs, the ligand has several notworthy features: it can be readily prepared in just two steps, is an air-stable crystalline solid, and provides optimal performance at ambient temperature.

The development of catalysts for the copper-catalyzed asymmetric addtion of diorganozincs to enones has recently received increased attention. Following the seminal discovery of Alexakis,[1] several groups have reported effective ligand systems for various structural classes of enones.[2] Most notably, Hoveyda and co-workers have introduced a new family of ligands that allow the highly enantioselective reactions of a wide variety of both cyclic and acyclic enones and cyclic nitroalkenes.[3] We have initiated our own investigation into this important carbon−carbon bond-forming reaction and report herein a new ligand that achieves good to excellent enantioselectivities with a range of cyclic enones. Notably, the ligand is an easily prepared air-stable crystalline solid that provides optimal results at ambient temperature.

Our investigations began with the preparation of a set of phosphine sulfonamide ligands derived in two steps from amino alcohols (Scheme 1).[4] Thus, treatment of either valinol or *tert*-leucinol with *p*-toluenesulfonyl chloride (TsCl), methane-sulfonyl chloride (MsCl), or trifluoromethane-sulfonic anhydride (Tf$_2$O) produced sulfonyl aziridines **1a**−**e**. Treatment of aziridines **1** with LiPPh$_2$ produced ligands

---

[1] Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427−2430.

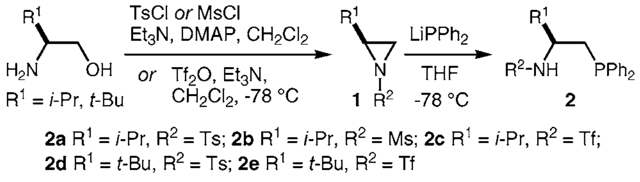
[2] (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (b) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518−3521. (c) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263. (d) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699−3702. (e) Liang, L.; Au-Yeung, T. T.-L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799−3801. (f) Zhou, H.; Wang, W.-H.; Fu, Y.; Xie, J.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2003**, *68*, 1582−1584. For recent reviews, see: (g) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196. (h) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (i) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 224−258.

[3] (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (b) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (c) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. (d) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363.

[4] This class of ligand is known and has been investigated in several asymmetric catalytic reactions. See: (a) Okada, T.; Morimoto, T.; Achiwa, K. *Chem. Lett.* **1990**, 999−1002. (b) Sakuraba, S.; Awano, K.; Achiwa, K. *Synlett* **1994**, 291−292. (c) Sakuraba, S.; Okada, T.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 927−934. (d) Hiroi, K.; Hidaka, A.; Sezaki, R.; Imamura, Y. *Chem. Pharm. Bull.* **1997**, *45*, 769−777. (e) Gustafsson, M.; Bergqvist, K.-E.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1452−1457.

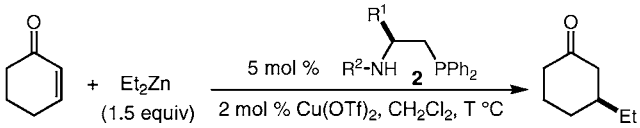
10.1021/ol034983r CCC: $25.00

Scheme 1



2a−**e** in good overall yield for the straightforward two-step sequence. In the case of **2e** (R^1 = t-Bu, R^2 = Tf) no chromatography is required and the ligand may simply be recrystallized from hexanes to give **2e** in 56% overall yield.

Table 1. Optimization of Ligand and Reaction Conditions

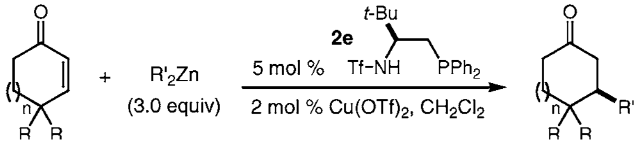


entry	ligand	R^1	R^2	temp (°C)	ee[a]
1	**2a**	i-Pr	Ts	−20	50
2	**2c**	i-Pr	Tf	−20	80
3	**2c**	i-Pr	Tf	−78	52
4	**2c**	i-Pr	Tf	23	88
5	**2b**	i-Pr	Ms	23	31
6	**2d**	t-Bu	Ts	23	82
7	**2e**	t-Bu	Tf	23	95
8[b]	**2e**	t-Bu	Tf	23	97

[a] Enantiomeric excess determined by chiral GLC (CDGTA). [b] Reaction run with 3.0 equiv of Et$_2$Zn.

With a set of ligands in hand, their performance in the reaction of Et$_2$Zn with cyclohexenone was evaluated (Table 1). Employing Cu(OTf)$_2$ (2 mol %) as the catalyst precursor, ligand **2a** (5 mol %) provided the conjugate addition product in 50% ee (entry 1). The substitution of triflamide for tosyl amide (ligand **2c**) led to a more selective reaction (80% ee; entry 2). We were then surprised to discover an unusual relationship between temperature and enantioselectivity: whereas at −78 °C, ligand **2c** provided only 52% ee, 88% ee was recorded at ambient temperature (entries 3 and 4).[5] At higher temperatures still (e.g., 38 °C), the ee is lower (85%); thus, the enantioselectivity is at its maximum at ambient temperature. Methane sulfonamide **2b** was then evaluated and provided poor results (entry 5). We then turned to the *tert*-leucinol-derived ligands **2d** and **2e**. Consistent with the above results, triflamide **2e** proved to be superior to tosyl amide **2d** and at ambient temperature provided the product in 95% ee (entries 6 and 7). Additional optimization revealed that the ee could be raised to 97% by employing 3.0 equiv of Et$_2$Zn (entry 8).

Table 2. Enantioselective Cu-Catalyzed Conjugate Addition of Dialkylzincs to Cyclic Enones at Ambient Temperature

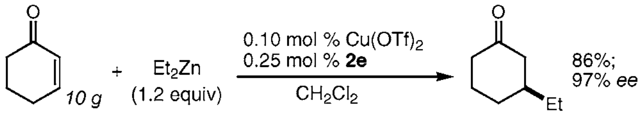


entry	n	R	R′	method[a]	t (h)	yield (%)[b]	ee[c]
1	0	H	i-Pr	A	0.25	64	86
2	0	Me	Et	B	24	58	84
3	1	H	Et	B	2	83	97
4[d]	1	H	n-Bu	A	4	52	94
5[d]	1	H	i-Pr	A	0.5	89	96
6	1	Me	Et	B	24	90	97
7	2	H	Et	B	3	67	97
8[d]	2	H	i-Pr	A	1	76	88

[a] Method A: R′$_2$Zn added after enone. Method B: R′$_2$Zn added before enone. [b] Isolated yield. [c] Enantiomeric excess determined by chiral GLC (CDGTA). [d] Reaction run with 1 mol % Cu(OTf)$_2$.

With ligand **2e** identified as the most effective, a survey of the reaction scope was then undertaken (Table 2). During these studies, it was noted that small but significant (and reproducible) differences in the enantioselectivities were recorded based on order of addition of the reagents (methods A and B). 2-Cyclopenten-1-one substrates reacted to give good enantioselectivities and moderate yields of the alkylated products (entries 1 and 2). 2-Cyclohexen-1-ones consistently engaged in highly enantioselective reactions with a range of dialkylzinc reagents (entries 3−5), albeit not with dimethylzinc, the use of which led to poor reaction performance. As with the cyclopentenone substrates, γ,γ-dialkyl substitution is well-tolerated (entry 6). Finally, 2-cyclohepten-1-one may be alkylated with high levels of enantioselectivity (entries 7 and 8). Thus, ligand **2e** shows encouraging generality with respect to a range of cyclic enone structures, and it is noteworthy that ligand **2e** consistently provides the highest enantioselectivities recorded to date with i-Pr$_2$Zn (entries 1, 5, and 8).

Scheme 2



We have optimized the reaction of 2-cyclohexen-1-one on a larger scale (10 g, 104 mmol) and were delighted to find that the reaction performed well with only 1.2 equiv of Et$_2$Zn and that the Cu(OTf)$_2$ loading could be dropped to 0.10 mol % and the ligand **2e** loading to 0.25 mol %. Under these conditions, the reaction was complete in <1.5 h, and the product was isolated in 86% yield and 97% ee. Apart from the use of a slight excess of Et$_2$Zn, it is difficult to imagine a more ideal process in terms of experimental ease, efficiency, and practicality.

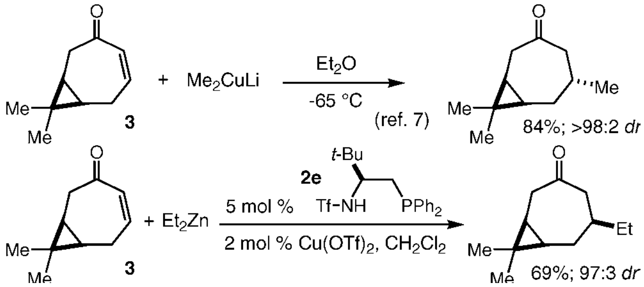
An interesting promise of asymmetric catalysis is the possibility of overriding an inherent bias in a chiral substrate,

---

[5] Hoveyda has documented a similar effect in the reactions of acyclic enones. See ref 3b.

allowing access to diastereomers that might otherwise be difficult to obtain. This, of course, is exactly the opposite of what is required for an effective kinetic resolution,[6] but it may be argued that this is more useful than kinetic resolution in cases where the racemic starting material is not extraordinarily inexpensive. The addition of Me_2CuLi to enone **3** has been reported to give the *trans* product exclusively,[7] and we have confirmed this result (Scheme 3). In contrast, subjection of **3** to the reaction with Et_2Zn catalyzed by $Cu(OTf)_2$/**2e** led to the smooth production of the *cis* product in 69% yield and 97:3 dr.[8]

Scheme 3



One of the more intriguing and practical aspects of this chemistry is the observation of maximum enantioselectivity at ambient temperature. We have examined this phenomenon in more detail and have found that it is highly dependent on the ligand:Cu ratio (Figure 1). For the reaction of 2-cyclohexen-1-one with Et_2Zn (employing ligand **2e**), a series of experiments was carried out varying the ligand:Cu ratio both at ambient temperature and at −20 °C. Whereas at ambient temperature, the ee of the reaction asymptotically approached a maximum value at higher ligand:Cu ratios, at −20 °C, radically different results were observed. Thus, even at ligand:Cu ratios less than 1, high enantioselectivity was maintained, while at ratios greater than 2, a large decrease in enantioselectivity was recorded.

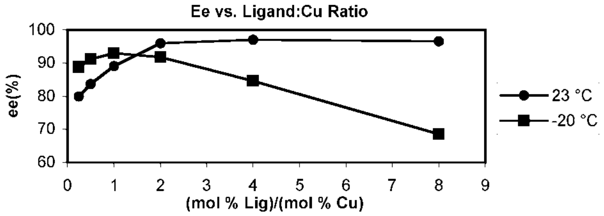


Figure 1. Enantioselectivity vs ligand/Cu at −20 and 23 °C.

On the basis of these data, it is reasonable to propose that at low ligand:Cu ratios, the same catalyst species is operative at both temperatures. The observation of similar negative nonlinear effects (2:1 ligand/Cu) at both temperatures supports this hypothesis.[9] More interestingly, it is clear that at high ligand:Cu ratios, a distinct and less highly enantioselective catalyst species is accessed at −20 °C, but not at ambient temperature.

A simple new ligand for the enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents to cyclic enones has been developed. This ligand is unique in consistently providing maximum enantioselectivity at room temperature. Combined with its ease of preparation, a high level of practicality has been established. Our current focus is on further development of this ligand class and investigation of its utility with nucleophiles other than organozincs.

Acknowledgment. We are grateful to Merck Research Laboratories for financial support. J.L.L. is a recipient of a Pfizer Award for Creativity in Organic Chemistry.

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

OL034983R

---

[6] A kinetic resolution of chiral 2-cyclohexenones based on this type of reaction has been reported. See: Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 927−930.

[7] Satoh, T.; Kaneko, Y.; Okuda, T.; Uwaya, S.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 3452−3460.

[8] Feringa has reported examples of catalyst control with chiral enones. No measure of the “intrinsic” diastereofacial bias of these enones was reported. See: Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2001**, *57*, 2485−2489.

[9] For a comprehensive review on nonlinear effects, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2952.