Asymmetric Conjugate Addition

Cu-Catalyzed Enantioselective Conjugate Additions of Alkyl Zinc Reagents to Unsaturated *N*-Acyloxazolidinones Promoted by a Chiral Triamide Phosphane**

*Alexander W. Hird and Amir H. Hoveyda**

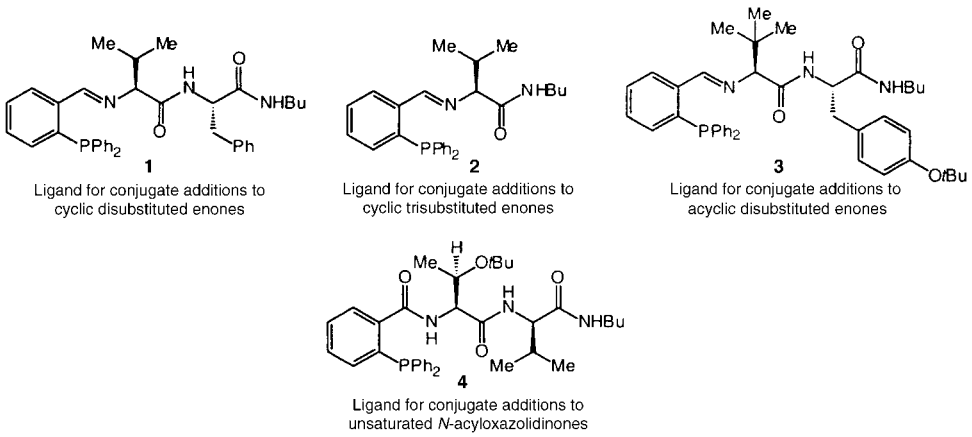
An area of recent interest in organic synthesis involves the development of protocols for efficient catalytic asymmetric conjugate additions (ACAs) of alkyl metal compounds to

[*] Prof. A. H. Hoveyda, A. W. Hird
Department of Chemistry, Merkert Chemistry Center
Boston College
Chestnut Hill, MA 02467 (USA)
Fax: (+1) 617-552-1442
E-mail: amir.hoveyda@bc.edu

[**] This research was supported by the United States National Institutes of Health (GM-47480).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  0044-8249/03/11511-1314 $ 20.00+.50/0

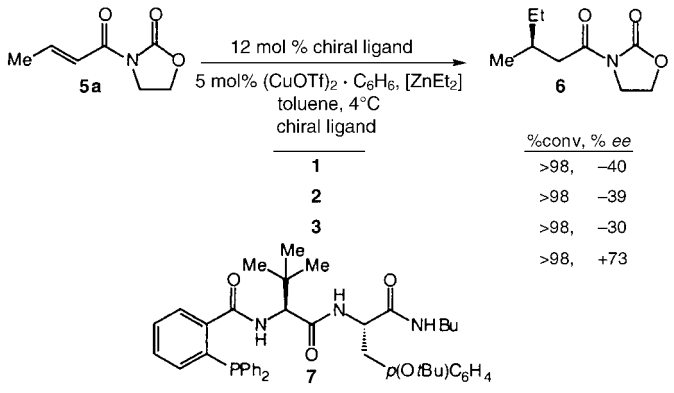


Scheme 1. Chiral amino acid-based phosphane ligands for Cu-catalyzed asymmetric conjugate additions (ACAs) to unsaturated carbonyls.

unsaturated carbonyls.[1] In these laboratories, we have been able to introduce methods for uniquely efficient and enantioselective catalytic ACAs of alkyl zinc reagents (not only [$ZnEt_2$]) to cyclic enones including unactivated cyclopentenones,[2] acyclic enones,[3] and trisubstituted exocyclic unsaturated ketones.[4] These investigations benefited from the modularity of the amino acid based ligands and parallel screening strategies,[5] as each of the above three sets of enone substrates requires a different optimal ligand (Scheme 1).

From the point of synthetic utility, in spite of recent advances outlined by various research groups, several critical problems remain to be addressed. One is in connection to the availability of a general approach to catalytic ACAs of alkyl groups to unsaturated esters,[6] amides, acids, or aldehydes. It was towards this end that we set out to develop catalytic ACAs of alkyl zinc reagents to unsaturated *N*-acyloxazolidinones;[7] the lure of such an approach is that enantioenriched β-alkyl carbonyls can be converted into an assortment of carboxylic acid and related derivatives. An efficient Cu-catalyzed method for ACA of alkyl zinc compounds to α,β-unsaturated oxazolidinones is disclosed herein.

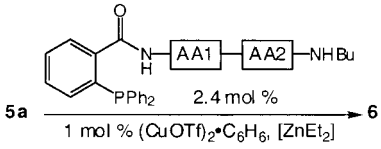
To initiate our studies, we examined the ability of **1**–**3** (Scheme 1), the three chiral ligands that effect the aforementioned catalytic ACA,[2–4] in promoting additions to oxazolidinone **5a** (Scheme 2). As the data in Scheme 2 indicate, these Schiff bases promote facile but relatively nonselective reactions. We then conducted a brief survey of different forms for the phosphane attachment to the amino acid moieties (that is, the derived amines and amides). This led us to determine that, in contrast to the previous studies, it is a triamide ligand (**7**, Scheme 2) that delivers product **6** with appreciable enantioselectivity.



Scheme 2. Results of initial ligand screening.

We then performed screening studies to identify the optimal amino acid moieties of amide phosphanes (**5a**→**6** used as the representative process).[8] These investigations indicated that subtle amino acid modifications can lead to substantial variations in enantioselection (for example, see entries 1–2, Table 1) and that a comprehensive screening process should be carried out to find a more optimal ligand. More importantly, and somewhat to our surprise, we also established that peptidic ligands bearing a D and an L amino acid may prove to be superior (see entries 3–4, Table 1).

Table 1: Amino acid modifications to **5a**.[a]

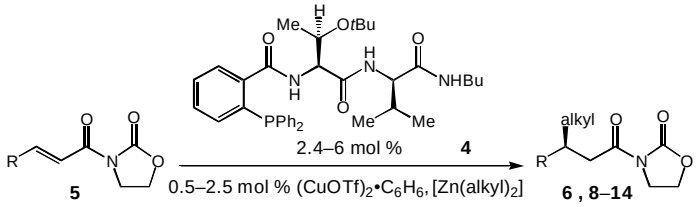


Entry	AA1	AA2	% *ee*
1	L-Phe	L-Phe	−34
2	L-Cha	L-Phe	+45
3	L-Val	L-Phe	+12
4	D-Val	L-Phe	−74

[a] All reactions have >98% conversion.

Subsequent screening of parallel libraries of ligands bearing both L,L- and D,L-dipeptides (approximately 100 ligands) led us to determine that treatment of **5a** with 1.0 mol% $(CuOTf)_2{\cdot}C_6H_6$, 2.4 mol% phosphane amide **4** (Scheme 1) and [$ZnEt_2$] (0°C, 1.3 h) leads to the formation of **6** in 95% *ee* and 95% yield (entry 1, Table 2).[9] It should be noted that ligand **4** has two unique structural attributes compared to the previous ligands used in reactions promoted by related peptidic systems.[2–4,10] Phosphane **4** is a triamide (not a diamide Schiff base or amine), and bears an L and a D amino

Table 2: Cu-catalyzed ACA of alkyl zinc reagents to unsaturated oxazolidinones.[a]

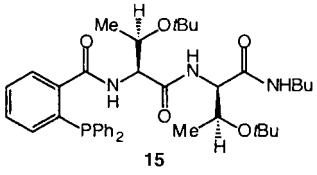


Entry	R	$[Zn(alkyl)_2]$	Product	Mol% **4**	Mol% Cu salt	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Me **a**	$[ZnEt_2]$	**6**	2.4	1.0	1.3	95	95
2	Me **a**	$[Zn\{iPr(CH_2)_3\}_2]$	**8**	5.0	1.0	12	61	93
3	Me **a**	$[Zn(iPr)_2]$	**9**	2.4	0.5	15	95	76
4	*n*Pr **b**	$[ZnEt_2]$	**10**	2.4	1.0	3	86	94
5	*n*Pr **b**	$[Zn\{iPr(CH_2)_3\}_2]$	**11**	2.4	1.0	24	89	95
6[d]	*n*Pr **b**	$[ZnMe_2]$	**12**	6.0	2.5	144	68	97
7	$(CH_2)_3$OTBS **c**	$[ZnEt_2]$	**13**	2.4	1.0	6	95	>98
8	*i*Pr **d**	$[ZnEt_2]$	**14**	2.4	1.0	24	88	92

[a] Conditions: 3 equiv dialkyl zinc reagent (10 equiv in entry 6), toluene, 0°C (−15°C for entry 6). [b] Yields after silica gel chromatography. All reactions proceeded to at least 95% conversion (GLC analysis). [c] All enantioselectivities determined by chiral GLC (β-DEX column for entries 1–6 and 8, CDGTA column for entry 7). [d] Phosphane **15** used as ligand.

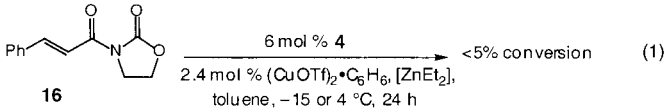
acid (not two L or D amino acids). The highest selectivity obtained for formation of **6** from an L,L ligand was 82% *ee* (AA1 = L-Asn(Trt), AA2 = L-Phe).

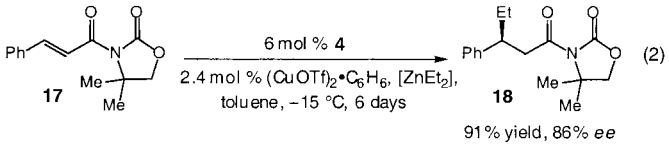
As indicated by the results summarized in Table 2, a range of unsaturated carbonyls and various alkyl zinc reagents can be used to access β-alkyl *N*-acyloxazolidinones in high yield and excellent enantioselectivity. The requisite unsaturated carbonyl substrates are accessed through olefin cross-metathesis promoted by a commercially available (Aldrich) catalyst developed in these laboratories.[11] As an example, **5c** (entry 7, Table 2) was prepared in this fashion in 94% yield. Furthermore, Cu-catalyzed ACA reactions can be carried out with the commercially available $(CuOTf)_2$·PhMe (Aldrich, used without purification). Conversion of **5a** into **6** is effected in the presence of 1 mol% $(CuOTf)_2$·PhMe and 2.4 mol% **4** to give **6** in 91% *ee* and 88% yield (>98% conversion, 4 h).[12] However, conjugate additions with $[ZnMe_2]$ (for example, entry 6, Table 2) are slower than those with longer chain alkyl zinc reagents and extended reaction times are needed.[13] In transformations involving $[ZnMe_2]$, superior efficiency is observed when **15** is used as the chiral ligand instead of **4** (68% versus 43% yield under identical conditions, shown in entry 6 of Table 2).



15

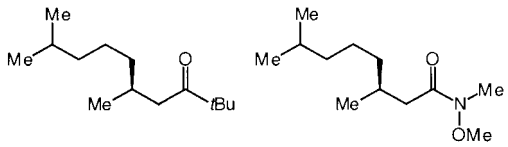
As shown in Equation (1), substrate **16** is inert to Cu-catalyzed ACA conditions. The derived dimethyloxazolidinone **17** can however be converted, albeit slowly, into **18** in 86% *ee* and 91% yield [Eq. (2)]. Control experiments[14] indicate that this difference in reactivity is most likely to



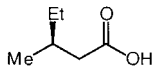


arise from the higher solubility of **17** under the reaction conditions and not as a result of variations in equilibrium between *s-cis* and *s-trans* conformers.[7]

Optically enriched β-alkyl *N*-acyloxazolidinones may be converted into other carbonyl derivatives that are not yet accessible directly through catalytic ACA reactions. Three representative examples are given below. Ketone **19** is formed in 93% *ee* through treatment of **8** (entry 2, Table 2) with *t*BuLi (THF, −20 to 0°C). It should be noted that Cu-catalyzed ACAs to acyclic *tert*-butyl enones proceed with only moderate levels of enantioselectivity (no greater than 75% *ee*).[4] Weinreb amide **20**, also obtained from **8** ($[AlMe_3]$, MeONHMe·HCl)[15] and acid **21** derived from **6**



19 81% (93% *ee*) from **8** **20** 74% (93% *ee*) from **8**



21 >98% (95% *ee*) from **6**

  0044-8249/03/11511-1316 $ 20.00+.50/0

($LiOH$, H_2O_2, THF)[16] can be converted into the corresponding aldehydes and a number of other carbonyl derivatives.

In conclusion, we have developed efficient Cu-catalyzed ACA reactions that are promoted by no more than 5 mol % of a readily accessible catalyst and deliver, in high enantiomeric purity, compounds that cannot be easily prepared by alternative catalytic protocols. This study introduces an amino acid based phosphane amide (versus Schiff base or amine systems) as an effective chiral ligand for asymmetric conjugate addition, and further demonstrates the important utility of this class of modular ligands.[17] The present method complements the previously reported catalytic ACA protocols[1–4,6] and should find utility in enantioselective organic synthesis.

Received: December 4, 2002 [Z50699]

Keywords: alkyl metal compounds · asymmetric catalysis · conjugate addition · copper · enantioselectivity

[1] For reviews on asymmetric conjugate additions of alkyl metal compounds to unsaturated carbonyls, see: a) N. Krause, A. Hoffmann-Roder, *Synthesis* **2001**, 171 – 196; b) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221 – 3236; c) B. L. Feringa, R. Naasz, R. Imbos, L. A. Arnold, *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 224 – 258; for representative recent advances, see: d) X. Hu, H. Chen, X. Zhang, *Angew. Chem.* **1999**, *111*, 3720 – 3723; *Angew. Chem. Int. Ed.* **1999**, *38*, 3518 – 3521; e) Y. Yamanoi, T. Imamoto, *J. Org. Chem.* **1999**, *64*, 2988 – 2989; f) L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. de Vries, R. Naasz, B. L. Feringa, *Tetrahedron* **2000**, *56*, 2865 – 2878; g) I. H. Escher, A. Pfaltz, *Tetrahedron* **2000**, *56*, 2879 – 2888; h) C. Borner, M. R. Dennis, E. Sinn, S. Woodward, *Eur. J. Org. Chem.* **2001**, 2435 – 2446; i) I. Chataigner, C. Gennari, S. Ongeri, U. Piarulli, S. Ceccarelli, *Chem. Eur. J.* **2001**, *7*, 2628 – 2634; j) A. Alexakis, G. P. Trevitt, G. Bernardinelli, *J. Am. Chem. Soc.* **2001**, *123*, 4358 – 4359; k) R. Shintani, G. C. Fu, *Org. Lett.* **2002**, *4*, 3699 – 3702; l) L. A. Arnold, R. Naasz, A. Minaard, B. L. Feringa, *J. Org. Chem.* **2002**, *67*, 7244 – 7254; m) L. Liang, T. T. L. Au-Yeung, A. S. C. Chan, *Org. Lett.* **2002**, *4*, 3799 – 3801.

[2] S. J. Degrado, H. Mizutani, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 755 – 756.

[3] H. Mizutani, S. J. Degrado, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 779 – 781.

[4] a) S. J. Degrado, H. Mizutani, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 13362 – 13363; for a related process involving cyclic nitroalkenes, see: b) C. A. Luchaco-Cullis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 8192 – 8193.

[5] a) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885 – 1889; for reviews regarding screening strategies for optimal catalyst identification, see: b) M. B. Francis, T. F. Jamison, E. N. Jacobsen, *Curr. Opin. Chem. Biol.* **1998**, *2*, 422 – 428; c) H. B. Kagan, *J. Organomet. Chem.* **1998**, *567*, 3 – 6; d) K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Curr. Opin. Chem. Biol.* **1999**, *3*, 313 – 319; e) B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 2648 – 2689; *Angew. Chem. Int. Ed.* **1999**, *38*, 2494 – 2532; f) M. L. Snapper, A. H. Hoveyda, *Combinatorial Chemistry* (Ed.: H. Fenniri), Oxford University Press, Oxford, **2000**, pp. 433 – 455.

[6] For a study on Cu-catalyzed asymmetric conjugate additions to alkylidene malonates, where only low-to-moderate selectivities (5–73 % *ee*) are obtained, see: A. Alexakis, C. Benhaim, *Tetrahedron: Asymmetry* **2001**, *12*, 1151 – 1157.

[7] For enantioselective conjugate additions of sterically hindered (*t*Bu and cyclohexyl) radicals to unsaturated *N*-acyloxazolidinones, see: a) M. P. Sibi, J. Ji, J. H. Wu, S. Gurtler, N. A. Porter, *J. Am. Chem. Soc.* **1996**, *118*, 9200 – 9201; b) M. P. Sibi, J. Ji, *J. Org. Chem.* **1997**, *62*, 3800 – 3801.

[8] Since control experiments showed that with Gly as AA3, the phosphane corresponding to **7** affords less than 20 % *ee* (**5a**→**6**), a new route for synthesis of ligand libraries with *n*Bu termini was developed and utilized. See the Supporting Information for details.

[9] See the Supporting Information for details of the screening studies.

[10] For example, see: a) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776 – 1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668 – 1671; b) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. G. Wirschun, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284 – 4285; c) C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy, A. H. Hoveyda, *Angew. Chem.* **2001**, *113*, 1504 – 1508; *Angew. Chem. Int. Ed.* **2001**, *40*, 1456 – 1460; d) J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *J. Am. Chem. Soc.* **2001**, *123*, 984 – 985; e) H. Deng, M. P. Isler, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2002**, *114*, 1051 – 1054; *Angew. Chem. Int. Ed.* **2002**, *41*, 1009 – 1012.

[11] a) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168 – 8179, and references therein; for applications to catalytic cross-metathesis, see: b) J. Cossy, S. BouzBouz, A. H. Hoveyda, *J. Organomet. Chem.* **2001**, *624*, 327 – 332; c) S. Randl, S. Gessler, H. Wakamatsu, S. Blechert, *Synlett* **2001**, 430 – 432.

[12] Cu-catalyzed ACA of the *cis* isomer of **5a** with [$ZnEt_2$] affords the opposite enantiomer of **6** in 69 % yield and only 64 % *ee*.

[13] Reactions with [$ZnMe_2$] are carried out at lower temperatures, since transformations performed at 4 °C, which also proceed at a significantly slower pace than other alkyl zinc reagents, lead to the formation of unidentified products.

[14] Reactions of various unsaturated dimethyl oxazolidinones corresponding to substrates in Table 2 leads to significantly slower rates of reaction.

[15] A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, *18*, 4171 – 4172.

[16] D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*, 6141 – 6144.

[17] A. H. Hoveyda, *Handbook of Combinatorial Chemistry*, (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**, pp. 991 – 1016.