Angew. Chem. **2000**, *112*, 3140 – 3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 – 3043.
[2] B. Alexander, D. S. La, D. R. Cefalo, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 4041 – 4042.
[3] S. Zhu, D. R. Cefalo, D. S. La, J. Y. Jamieson, W. M. Davis, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1999**, *121*, 8251 – 8259.
[4] a) D. S. La, J. B. Alexander, D. R. Cefalo, D. D. Graf, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **1998**, *120*, 9720 – 9721; b) J. B. Alexander, R. R. Schrock, W. M. Davis, K. C. Hultzsch, A. H. Hoveyda, J. H. Houser, *Organometallics* **2000**, *19*, 3700 – 3715; c) G. S. Weatherhead, J. H. Houser, J. G. Ford, J. Y. Jamieson, R. R. Schrock, A. H. Hoveyda, *Tetrahedron Lett.* **2000**, *41*, 9553 – 9559.
[5] a) D. S. La, J. G. Ford, E. S. Sattely, P. J. Bonitatebus, Jr., R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 11 603 – 11 604; b) G. S. Weatherhead, J. G. Ford, E. J. Alexanian, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 1828 – 1829; c) D. R. Cefalo, A. F. Kiely, M. Wuchrer, J. Y. Jamieson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, in press.
[6] Optically pure binaphthol (both antipodes) is commercially available from Kankyo Kagaku Center Co., Ltd. at approximately one U.S. dollar per gram.
[7] The PtO_2 catalyst was recovered and reused in three additional 20 g scale reactions without significant loss of activity. For the original hydrogenation procedure, see: D. S. Lingenfelter, R. C. Helgeson, D. J. Cram, *J. Org. Chem.* **1981**, *46*, 393 – 406.
[8] Catalytic hydrogenation under lower pressures of H_2 are significantly slower (e.g., consumption of **4** after one week at 45 psi (310 kPa, 3 atm)) and some partially hydrogenated product is often present.
[9] Optically pure **5** is available from Kankyo Kagaku Center, but at nearly ten times the cost of (*R*)- or (*S*)-**4**.
[10] To establish the enantiopurity of dialkylation product (*R*)-**6** and its corresponding diol, the derived mentholate phosphate was prepared and its ^{31}P NMR spectrum was compared to that of a sample of *rac*-phosphate. The spectrum of a racemic sample exhibits two resonances at $\delta = 144.4$ and 139.2 (1:1 ratio); that of (*R*)-phosphate contains a single resonance at $\delta = 144.9$. Oxidation to the corresponding phosphonate and comparison of its ^{31}P NMR spectrum to that of the corresponding racemic mixture was carried out as well ($\delta = -4.9$ and -3.3 for the *rac* sample and -4.9 for the (*R*)-isomer).
[11] Protonated (*R*)-**6** may also be treated with two equivalents of benzyl potassium and one equivalent of Mo triflate **7** (22 °C, THF) to afford optically pure (*R*)-**3** in 41 % isolated yield after purification.
[12] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155703. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[13] Values for k_{sa} (determined at 10 °C intervals from 0 to 30 °C) were used to establish the activation parameters for **3** from an Eyring plot ($R^2 = 0.994$); these calculations give $\Delta H^{\ddagger} = 15.7(0.9)$ kcal mol^{-1} and $\Delta S^{\ddagger} = -8(3)$ kcal K^{-1} mol^{-1}).
[14] The variable temperature ^1H NMR spectra of **3** with one equivalent of MeCN indicates the presence of all four possible **3**·MeCN diastereomers (−60 °C). There is a notable downfield shift of the alkylidene H resonance of the less Lewis acidic *syn* isomer as the temperature is lowered, indicating the weaker association of *syn* **3** with MeCN. The more Lewis acidic *anti* isomers require a higher temperature (~0 °C) for the same process to occur.
[15] For a comprehensive review of metal-catalyzed kinetic resolutions, see: A. H. Hoveyda, M. T. Didiuk, *Curr. Org. Chem.* **1998**, *2*, 537 – 574.
[16] Relative rates are calculated based on the equation reported by Kagan, see: K. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249 – 330.
[17] By dimeric product we mean the material obtained by catalytic intermolecular cross-coupling of two substrate molecules through their terminal alkenes.
[18] The reaction times with in situ **3** are longer (e.g., 2 h vs. 1 h for formation of (*R*)-**20**) because of the presence of the Lewis basic solvent THF. Typically the final ratio of THF:C_6H_6 is ~1:10.
[19] Treatment of **23** and the derived methoxymethyl (MOM) ether of **23** with styrene in the presence of 5 – 100 mol % of imidazolinium-containing Ru catalysts of Grubbs or Hoveyda at 22 or 75 °C (CH_2Cl_2 and $CHCl_3$) results in < 5 % conversion after 12 h. See: a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956; b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168 – 8179.
[20] This protocol is based on an original procedure by Koenigs and Carl, see: W. Koenigs, R. W. Carl, *Chem. Ber.* **1891**, *24*, 3889 – 3900.

Modular Pyridinyl Peptide Ligands in Asymmetric Catalysis: Enantioselective Synthesis of Quaternary Carbon Atoms Through Copper-Catalyzed Allylic Substitutions**

Courtney A. Luchaco-Cullis, Hirotake Mizutani, Kerry E. Murphy, and Amir H. Hoveyda*

Dedicated to Professor David A. Evans on the occasion of his 60th birthday

To develop a new transformation and achieve maximum levels of reactivity and selectivity, myriad reaction parameters must be explored and adjusted. In the context of establishing an effective catalytic enantioselective process,[1] the choice of an appropriate chiral ligand and metal salt is perhaps most crucial: a blend of mechanistic knowledge (e.g., details of coordination chemistry) and human intuition are typically used to identify a desirable metal – ligand combination. Such a task becomes significantly more facile if readily modifiable chiral ligands are at hand; depending on the nature of the metal salts involved and the type of transformation that is being developed, ligand structures may be altered so that reactivity and selectivity levels are improved. The latter approach is particularly attractive if identification of the lead candidates is accomplished through screening of ligand libraries.[2]

In the past few years we have studied and developed various peptide-based ligands that promote a range of catalytic asymmetric C–C bond-forming reactions. In all instances, optimal catalysts have been identified through examination of collections of peptide – metal complexes.[3–6] Peptidic structures represented by **I** (Figure 1) have been developed to initiate efficient and asymmetric Ti-catalyzed CN addition to epoxides[3] and imines.[4] Zr-catalyzed alkylation of imines has been demonstrated to proceed efficiently and with high asymmetric induction in the presence of ligands

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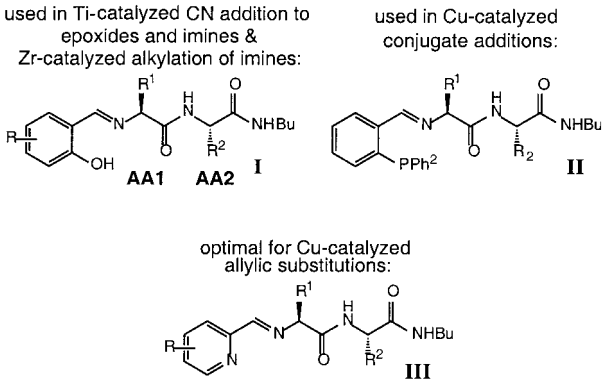


Figure 1. Various peptide-based chiral ligands used in catalytic asymmetric reactions involving early and late transition metals.

I or the corresponding peptidic amines.[5] Chiral phosphines **II** effect catalytic asymmetric conjugate additions to cyclic enones, where both the catalyst (CuOTf; OTf = trifluoromethanesulfonate) and the reagent (dialkylzinc reagents) are late transition metal complexes.[6] In every instance, readily modular and non-*C*2-symmetric[7] peptide-based chiral ligands have played a central role in establishing optimal reactivity and selectivity.

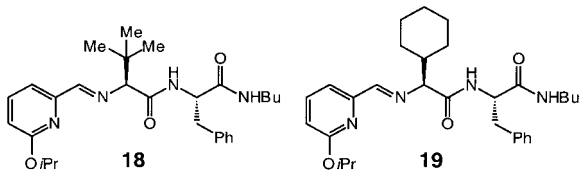
More recently, we set out to investigate the possibility of using peptidic ligands to promote enantioselective allylic substitutions. Largely because of the scarcity of related protocols, we are particularly interested in transformations that utilize the less explored "hard" alkylating agents[8] which enantioselectively deliver the problematic quaternary carbon centers.[9] Herein, we report the results of our studies regarding the development of Cu-catalyzed allylic substitutions, in which pyridinyl peptidic structures represented by **III** (Figure 1) emerge for the first time as the chiral ligands of choice. The catalytic enantioselective method described allows for the efficient, regio- and enantioselective formation of quaternary carbon centers from readily available substrates, catalysts, and alkylating agents.

We initiated our search for the optimal conditions by using the more reactive and readily accessible disubstituted olefins (vs. trisubstituted alkenes described below). Since CuCN exhibits a preference for the S_N2' mode of addition in related processes with Grignard reagents, it was selected for the preliminary optimization studies (in preference to copper halides or acetate).[10] Examination of potential substrates indicated that allylic phosphates are the most suitable starting materials (see Scheme 1).[11, 12] These electrophiles are inert to Et_2Zn but undergo alkylation in the presence of Cu salts in CH_2Cl_2, toluene, Et_2O, and THF. The corresponding chlorides react smoothly with Et_2Zn in CH_2Cl_2, toluene, or Et_2O ($-30\,^\circ C$, 18 h, without ligand and Cu salt) and the derived acetates, phenyl ethers, and phenyl carbamates afford $<10\,\%$ conversion, even in the presence of Cu salts (e.g., CuCN and CuCl). With the above parameters clarified, we turned our attention to the identification of optimal ligands. Related mechanistic work suggest that the Schiff base portion of the peptidic ligands is likely to be a metal-ligation site and is critical to reactivity and selectivity.[13] We therefore decided to perform catalyst optimization in the following order: 1) identify the optimal Schiff base type, 2) ascertain the identity of the most desirable Cu salt, 3) determine the optimal peptidic construct (e.g., di- or tripeptide), 4) further enhance the enantioselectivity through identification of the optimal Schiff base and amino acid moieties.

Chiral ligands **3**–**6** (Scheme 1) were prepared. Readily available L-Val and L-Phe served as the AA1 and AA2 and the Schiff base structure was altered. As shown in Scheme 1 (First Phase Screening), treatment of phosphate **1a** with Et_2Zn in the presence of 10 mol% CuCN and chiral ligands **3**–**6** in THF at $-30\,^\circ C$ leads to $>98\,\%$ conversion within 6 h. Pyridine dipeptide **6** delivers the highest level of enantioselectivity (34% *ee*), followed by phosphine **5** (26% *ee*). To ascertain the identity of the most efficient and selective ligand/Cu salt combination, formation of **2a** was examined in two sets of experiments involving ligands **5** and **6** and a collection of Cu salts (see Scheme 1, Second Phase Screening). This study established that **6** and CuCN, overall, provide the most efficient, regio- and enantioselective process.[14]

Next, we secured the following additional ligand attributes (Third Phase Screening, Scheme 1): 1) an amide terminus is critical to the enantioselectivity; replacement of the NHBu in **6** with an OMe group (**7**, Scheme 1) leads to a significant reduction of *ee*, 2) incorporation of a third amino acid (**8**, Scheme 1) or removal of one (**9**, Scheme 1) is detrimental to the enantioselectivity.[15] The stereochemical outcome from the reaction with **9** (14% *ee*) underlines the importance of the AA2 moiety and indicates that simple attachment of a chiral group to the pyridine ligation site is alone not sufficient for high asymmetric induction.

With the pyridinyl dipeptide framework emerging as the optimal construct, we prepared chiral ligands **10**–**17** (Scheme 1, Fourth Phase Screening) and examined their ability to initiate the enantioselective alkylation of **1a** under the same conditions mentioned above. Thus, the catalytic ability of the derived amine **10**, amide **11**, and various α-substituted pyridyl systems (**12**–**15**) were investigated; in addition, the related indole-based **16** and *C*2-symmetric **17** were probed. All reactions proceed to $>98\,\%$ conversion and exhibit high degrees of $S_N2':S_N2$ selectivity, but it is the α-substituted ligands **12**–**14** that generate the highest *ee*.



We thus selected *o*-O*i*Pr pyridine as the Schiff base moiety, and continued with the optimization of the AA1 and AA2 segments (see Figure 1) according to methods reported previously.[3] These studies uniformly suggest that L-Phe is the AA2 of choice, and that ligands that bear L-Val (**14**), L-*t*Leu (**18**), and L-Chg (**19**) at the AA1 position offer similarly superior enantioselection.[16] Chiral ligands **14**, **18**, and **19** (10 mol%) were subsequently used in catalytic alkylation of aryl olefins **1a**–**c** in the presence of Et_2Zn and 10 mol% CuCN in THF. The results shown in Table 1 indicate the ligands that provide the highest selectivity for a particular

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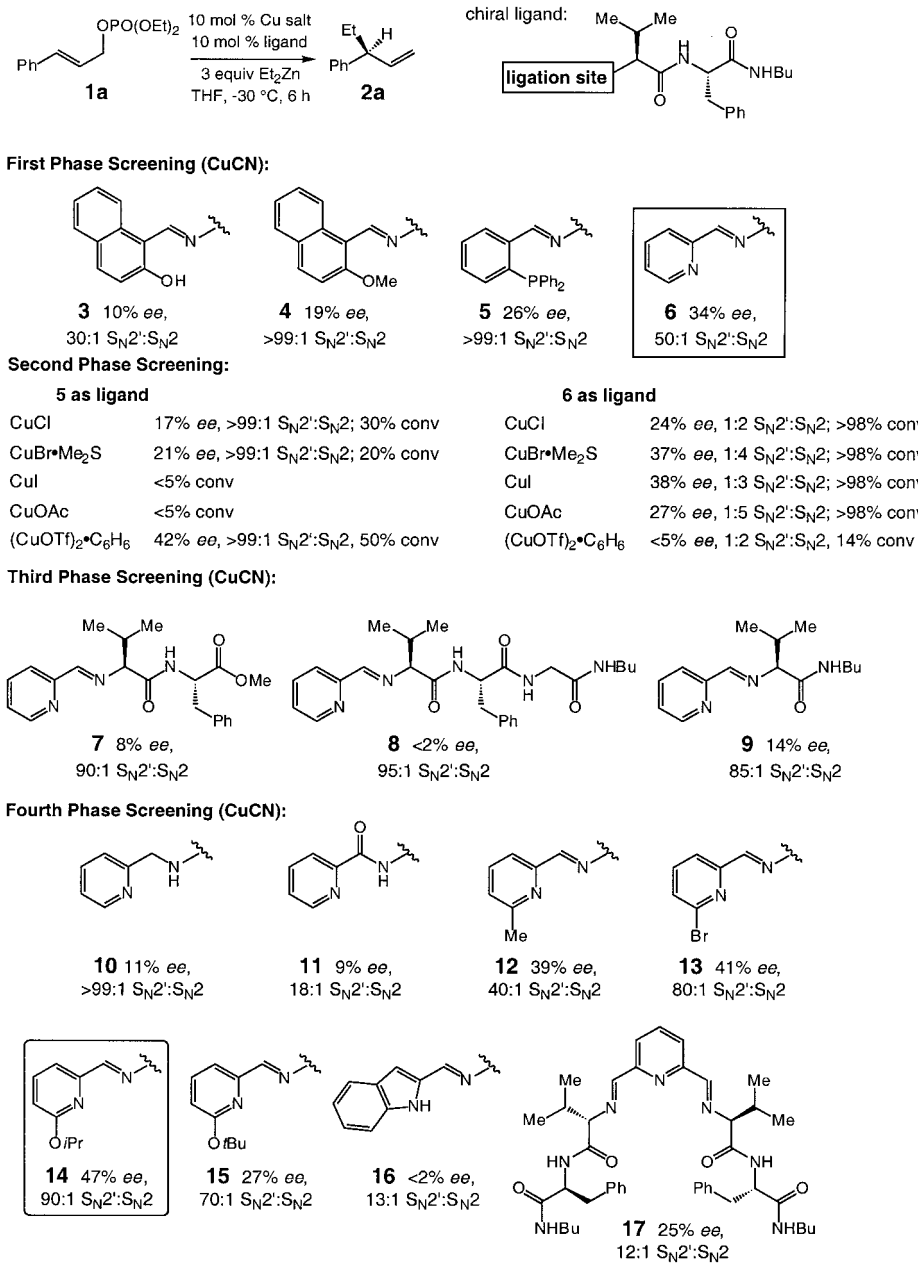
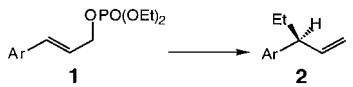


Scheme 1. Screening studies for optimization of ligand and Cu salt. (All conversions >98%, all yields ≥80%, unless otherwise noted.)

substrate. Thus, when alkylation is performed at −78 °C, **2a–c** are generated efficiently in 66%, 87%, and 75% *ee*, respectively (<2% S_N2 product).[17, 18] The selectivity and reactivity levels (Table 1) are competitive with the recently reported catalytic alkylations of allylic chlorides,[19] where sterically demanding dialkylzinc reagents (e.g., dineopentylzinc) are required for high enantioselectivity (≤50% *ee* with *n*-alkylzinc reagents).

At this point, we began to investigate Cu-catalyzed reactions of trisubstituted olefin substrates and the catalytic enantioselective synthesis of quaternary carbon centers. Catalytic alkylation of allylic phosphates **20a–e** (Table 2) in the presence of 10 mol% of chiral ligands **14**, **18**, and **19** and 10 mol% CuCN (Et_2Zn, −78 °C, THF) was investigated; all C–C bond-forming reactions occur efficiently and with excellent regiocontrol (<2% S_N2 product formed). Importantly, alkylation products **21a–e** are formed in 78–90% *ee* (Table 2);[20] the highest enantioselectivities are observed with substrates that bear electron-withdrawing aryl substituents (**20c–e**). The optimal chiral ligand varies depending on the starting material: Reaction of **20b** (entry 2, Table 2) in the presence of **14** and **18** affords **21b** in 72% and 69% *ee*, respectively (vs. 78% *ee* with **19**); catalytic alkylation of **20d** (entry 4, Table 2) with ligands **14** and **19** leads to the formation of **21d** in 83% and 81% *ee*, respec-

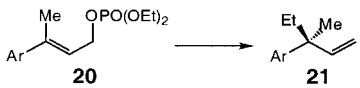
Table 1. Cu-catalyzed asymmetric allylic substitution of disubstituted alkenes.[a]



Entry	Aryl group		Ligand	Conv [%][b]	Yield [%][c]	*ee*[d] (config.)
1	Ph	**2a**	**19**	>98	34[e]	66 (+)
2	*o*NO_2Ph	**2b**	**18**	>98	85	87 (−)
3	*p*NO_2Ph	**2c**	**19**	>98	73	75 (+)

[a] Conditions: 10 mol% ligand, 10 mol% CuCN, 3.0 equivalents Et_2Zn, THF, −78 °C, 12 h. [b] Determined by analysis of the 400 MHz ^{1}H NMR spectrum. [c] Yields of isolated products after silica gel chromatography. [d] Determined by chiral gas–liquid chromatography (GLC) analysis (Chiraldex GTA for entries 1 and 2, Betadex 120 for entry 3). [e] Low yield is because of the volatility of product.

Table 2. Cu-catalyzed asymmetric allylic substitution of trisubstituted alkenes.[a]



Entry	Aryl group		Ligand	Conv [%][b]	Yield [%][c]	*ee*[d] (config.)
1	Ph	**20a**	**14**	>98	80	78 (+)
2	*o*OMePh	**20b**	**19**	>98	70	78 (+)
3	*p*NO_2Ph	**20c**	**18**	>98	80	86 (+)
4	*p*OTsPh	**20d**	**18**	>98	83	90 (+)
5	*p*CF_3Ph	**20e**	**14**	>98	59	81 (+)

[a] Conditions: Same as in Table 1, except 24 h. [b] Determined by analysis of the 400 MHz ^{1}H NMR spectrum. [c] Yields of isolated products after silica gel chromatography. [d] Determined by chiral GLC analysis (Chiraldex GTA for entry 1, Betadex 120 for entries 2, 3 and 5) and chiral high-performance liquid chromatography (HPLC; chiralcel OD for entry 4).

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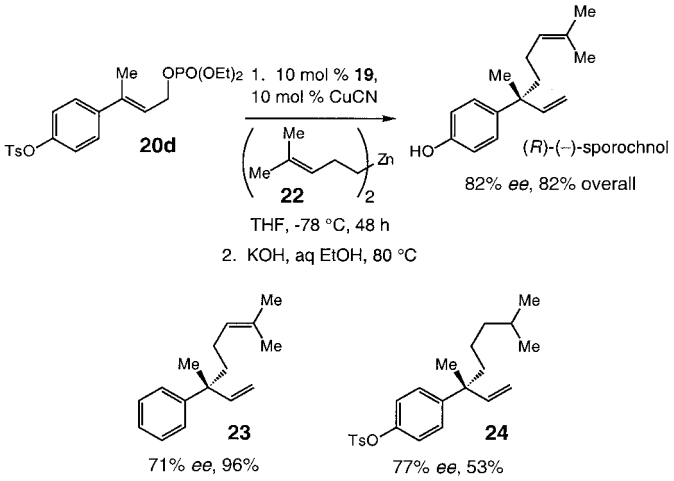
tively (vs. 90% *ee* with **18**). These results highlight the practical advantages of a readily modular class of chiral catalysts.

The method presented herein should prove to be of notable utility in natural product synthesis. The example shown in Scheme 2 is illustrative. The fish deterrent, sporochnol, has



Scheme 2. Cu-catalyzed asymmetric allylic substitution with longer-chain alkylzinc reagents and the total synthesis of sporochnol.

been prepared enantioselectively by the use of the Cu-catalyzed asymmetric process through a route that is significantly shorter than outlined previously.[21] This asymmetric synthesis demonstrates that the present method can be readily extended to other functionalized organozinc reagents (82% *ee* and 82% yield). There is another noteworthy feature of the catalytic alkylations in Scheme 2: the reaction of **20d** with alkylzinc **22** proceeds in the opposite stereochemical sense to the reaction with Et_2Zn (see entry 4, Table 2). The catalytic alkylation of **20a** with **22** leads to preferential formation of the *R* isomer of the desired product as well ((*R*)-**23** in 71% *ee*, 96% yield; compare to entry 1 in Table 2). Catalytic alkylation of **20d** with the corresponding saturated alkylzinc reagent also leads to preferential formation of (*R*)-**24** (77% *ee*, 53% yield; Scheme 2). The reversal of enantioselectivity is therefore not because of the electron-withdrawing OTs (Ts = 4-methylphenylsulfonyl) group and/or the alkene in **22**. Mechanistic studies to address whether the above selectivity trend is a result of the steric difference between the alkylzinc reagents (e.g., Et_2Zn vs. **22**) or other factors is in progress.[22]

In summary, we disclose a new class of peptide-based chiral ligands bearing a pyridinyl residue that is suitable for late transition metal binding and catalysis. Through synthesis and analysis of libraries, the modularity of these ligands can be exploited for the improvement of reaction efficiency as well as regio- and enantioselectivity. These attributes have been used in the development of a new class of catalytic asymmetric alkylation reactions that deliver quaternary carbon centers with high levels of site and enantiofacial control. Study of the mechanism, extension to reactions of aliphatic substrates, and further exploration of this and related classes of peptidic ligands in catalytic asymmetric synthesis are in progress.

Experimental Section

2-(6-Isopropoxy)-pyridine carboxaldehyde-L-Val-L-Phe-Bu (**14**). 2-(6-isopropoxy)-pyridine carboxaldehyde (0.10 g, 0.61 mmol) and anhydrous $MgSO_4$ (0.10 g) were added to a solution of H_2N-L-Val-L-Phe-Bu (0.19 g, 0.61 mmol) in CH_2Cl_2 (3.0 mL). The resulting mixture was stirred for 12 h at 22 °C. Filtration of solids and removal of volatiles in vacuo, followed by recrystallization from hot Et_2O delivered the pure product as a white solid (0.20 g, 0.43 mmol, 70%). IR(KBr): $\tilde{\nu}$ = 3298 (br), 2963 (m), 2932 (m), 2872 (w), 1646 (s), 1598 (m), 1567 (m), 1451 (s), 1323 (m), 1262 (m), 1116 (m), 1000 (m), 811 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (1H, s, pyrCHNR), 7.64 (1H, t, $^3J_{H,H}$ = 7.6 Hz, pyrH), 7.53 (1H, d, $^3J_{H,H}$ = 7.2 Hz, pyrH), 7.33–7.22 (6H, m, ArH and NH), 6.75 (1H, d, J = 8.0 Hz, pyrH), 5.87 (1H, br s, NH), 5.38–5.31 (1H, m, OC*H*$(CH_3)_2$), 4.64 (1H, dd, $^3J_{H,H}$ = 15.2, 7.6 Hz, C*H*CH_2Ph), 3.65 (1H, d, $^3J_{H,H}$ = 4.0 Hz, CH*i*Pr), 3.22–3.02 (4H, m, CHC*H*$_2$Ph and NHC*H*$_2(CH_2)_2CH_3$), 2.28–2.20 (1H, m, CHC*H*$(CH_3)_2$), 1.35 (6H, dd, $^3J_{H,H}$ = 6.0 Hz, OCH(C*H*$_3)_2$), 1.32–1.09 (4H, m, NHCH$_2$(C*H*$_2)_2CH_3$), 0.90–0.75 (9H, m, CHCH(C*H*$_3)_2$ and NHCH$_2(CH_2)_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 170.9, 164.3, 151.7, 139.4, 137.5, 129.9, 129.3, 127.5, 114.2, 114.0, 79.1, 68.8, 55.1, 39.9, 38.7, 33.8, 32.1, 22.9, 22.8, 20.7, 20.2, 18.0, 14.5; high resolution MS calcd for $C_{27}H_{38}N_4O_3$ [M+1]: 467.3022; found: 467.3023; elemental analysis calcd (%) for $C_{27}H_{38}N_4O_3$: C 69.50, H 8.21, N 12.01; found: C 69.22, H 7.93, N 11.91. $[\alpha]_D^{20}$ +1.77° (*c* 5.59, $CHCl_3$).

(+)-(S)-3-methyl-3-phenyl-1-pentene (**21a**). (CAUTION: Et_2Zn IS PYROPHORIC! USE EXTREME CAUTION!) A flame-dried 13 × 100 test tube was charged with CuCN (1.4 mg, 1.6×10^{-3} mmol), and **14** (7.6 mg, 1.6×10^{-3} mmol); the mixture was cooled to −78 °C and of a solution of 2-phenyl-4-(diethyl-phosphoryloxy)-2-butene (5.0×10^{-2} g, 0.16 mmol; 1.0 mL) in THF was then added. After equilibration of the reaction to −78 °C for 15 min, Et_2Zn (5.0×10^{-2} mL, 0.49 mmol) was added dropwise, at which point the solution turned bright red. The mixture was allowed to stir at −78 °C for 12 h, after which time the reaction was quenched through addition of a solution of HCl (1.0 mL, 10% by volume). Extraction with Et_2O (3 × 2.0 mL), removal of volatiles in vacuo, and purification of the resulting yellow oil through chromatography on silica gel (100% pentanes to 20:1 pentanes:Et_2O) afforded (*S*)-**21a** (20.5 mg, 80%). GLC analysis indicates that the enantiomeric ratio of the product is 89:11. IR (KBr): $\tilde{\nu}$ = 3089 (w), 3058 (w), 2976 (s), 2932 (m), 2882 (m), 1719 (w), 1638 (w), 1600 (w), 1499 (m), 1456 (m), 1380 (w), 1273 (w), 1003 (w), 921 (m), 771 (s), 708 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.15 (5H, m, ArH), 6.03 (1H, dd, $^3J_{H,H}$ = 17.7, 10.8 Hz, CC*H*CH_2), 5.10 (1H, dd, $^3J_{H,H}$ = 10.8, 1.2 Hz, CCHC*H*$_2$), 5.04 (1H, dd, $^3J_{H,H}$ = 17.4, 1.2 Hz, CCHC*H*$_2$), 1.80 (2H, dq, $^3J_{H,H}$ = 14.1, 7.8 Hz, CC*H*$_2$CH$_3$), 1.35 (3H, s, CCH_3), 0.77 (3H, t, $^3J_{H,H}$ = 7.2 Hz, CCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 148.0, 147.4, 128.6, 127.3, 126.2, 112.4, 45.3, 34.2, 25.2, 9.8; high resolution MS calcd for $C_{12}H_{16}$: 160.1252, found: 160.1250; elemental analysis calcd (%) for $C_{12}H_{16}$: C 89.94, H 10.06; found: C 89.74, H 9.99. $[\alpha]_D^{22}$ +4.53° (c 10.43, $CHCl_3$) for 78% *ee* sample.

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[1] *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] a) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885–1889; 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 in *Combinatorial Chemistry* (Ed.: H. Fenniri), Oxford University Press, Oxford, **2000**, pp. 433–455.

[3] 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) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1997**, *109*, 1781–1785; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704–1707.

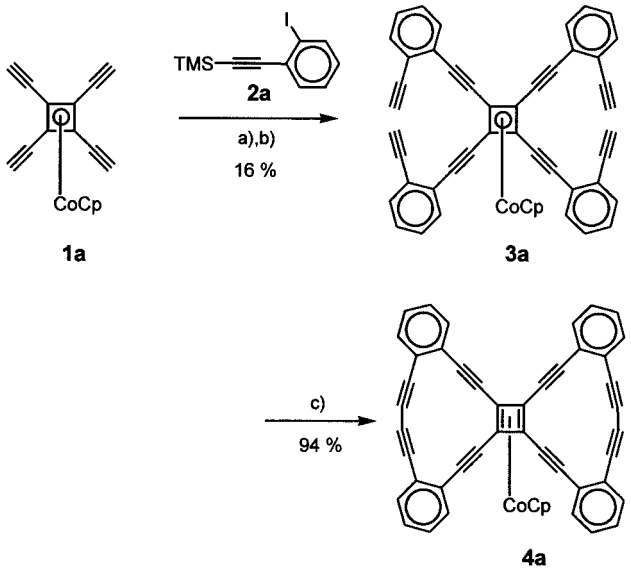
  0044-8249/01/11308-1507 $ 17.50+.50/0

[4] a) 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; b) J. R. Porter, W. G. Wirschun, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 2657 – 2658.
[5] J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *J. Am. Chem. Soc.* **2001**, *123*, 984 – 985.
[6] S. J. Degrado, H. Mizutani, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 755 – 756.
[7] For a recent review regarding the use of some non-*C*2-symmetric chiral ligands in metal-catalyzed enantioselective reactions, see: a) A. Pfaltz in *Stimulating Topics in Organic Chemistry* (Eds.: M. Shibasaki, J. F. Stoddart, F. Vögtle), VCH-Wiley, Weinheim, **2000**, pp. 89 – 103; b) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336 – 345.
[8] For previous work from these laboratories in connection to catalytic asymmetric allylic substitutions with hard alkylmetals and other related studies, see: a) A. H. Hoveyda, N. M. Heron in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 431 – 454. For a review concerning catalytic asymmetric addition of soft nucleophiles to olefins, see: b) B. M. Trost, V. L. van Vranken, *Chem. Rev.* **1996**, *96*, 395 – 422.
[9] For a review of catalytic enantioselective methods for the synthesis of quaternary carbon stereogenic centers, see: E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402 – 405; *Angew. Chem. Int. Ed.* **1998**, *37*, 388 – 401.
[10] a) C. C. Tseng, S. D. Paisley, H. L. Goering, *J. Org. Chem.* **1986**, *51*, 2884 – 2891; b) J.-E. Backvall, M. Sellen, B. Grant, *J. Am. Chem. Soc.* **1990**, *112*, 6615 – 6621.
[11] For Cu-catalyzed (nonasymmetric) addition of organotitanium and organozirconium reagents to allylic phosphates, see: a) A. Masayuki, E. Nakamura, B. H. Lipshutz, *J. Org. Chem.* **1991**, *56*, 5489 – 5491; b) L. M. Venanzi, R. Lehmann, R. Keil, B. H. Lipshutz, *Tetrahedron Lett.* **1992**, *33*, 5857 – 5860.
[12] For Cu-catalyzed asymmetric alkylation of an allylic phosphate with Grignard reagents, see: a) M. van Klaveren, E. S. M. Persson, A. del Villar, D. M. Grove, J.-E. Backvall, G. van Koten, *Tetrahedron Lett.* **1995**, *36*, 3059 – 3062. For W-catalyzed asymmetric alkylation of allylic phosphates with soft nucleophiles, see: b) G. C. Lloyd-Jones, A. Pfaltz, *Angew. Chem.* **1995**, *107*, 534 – 536; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 462 – 464.
[13] N. S. Josephsohn, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, unpublished results.
[14] As depicted in Scheme 1, the combination of **5** and $(CuOTf)_2 \cdot C_6H_6$, provides slightly higher enantioselectivity, but is less efficient than **6** and CuCN (50% vs. >98% conversion). Further examination of the former system is in progress.
[15] Tripeptide **8** and its derived Me ester afford similar results.
[16] When D-Val is used as AA1, the sense of enantioselection is reversed, indicating that the stereochemical identity of AA1 is critical to the sense of stereochemical induction and that the D,L-ligand may deliver lower levels of enantioselectivity than the L,L isomer.
[17] The absolute configuration of **2a** was determined to be *S* through comparison of its $[\alpha]_D$ value with those reported (authentic material was also prepared). See: T. Hayashi, T. Hagihara, Y. Katsuro, M. Kumada, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 363 – 364.
[18] The corresponding electron-rich *p*- and *o*-OMe substrates proved to be unstable.
[19] F. Dubner, P. Knochel, *Angew. Chem.* **1999**, *111*, 391 – 393; *Angew. Chem. Int. Ed.* **1999**, *38*, 379 – 381; b) F. Dubner, P. Knochel, *Tetrahedron Lett.* **2000**, *41*, 9233 – 9237. Moreover, in ref. [12b], a catalytic alkylation of **1a** with *n*BuMgCl to afford **2a** is reported to proceed in 10% *ee* (92% S_N2').
[20] Absolute configuration of **21a** was determined to be *S* by comparison of its $[\alpha]_D$ with those reported. See: H. Yamamoto, A. Yanagisawa, N. Nomura, Y. Yamada, H. Hibino, *Synlett* **1995**, 841 – 842.
[21] For previous enantioselective total syntheses of sporochnol, see: a) M. Takahashi, Y. Shioura, T. Murakami, K. Ogasawara, *Tetrahedron: Asymmetry* **1997**, *8*, 1235 – 1242; b) T. Kambikubo, M. Shimizu, K. Ogasawara, *Enantiomer* **1997**, *2*, 297 – 301; c) A. Fadel, L. Vandromme, *Tetrahedron: Asymmetry* **1999**, *10*, 1153 – 1162. For a review on asymmetric catalysis in target-oriented synthesis, see: A. H. Hoveyda in *Stimulating Topics in Organic Chemistry* (Eds.: F. Vögtle, J. F. Stoddart, M. Shibasaki), Wiley-VCH, Weinheim, **2000**, pp. 145 – 162.
[22] Reaction of di-2-methylpentylzinc (cf. **24**, Scheme 2) with **20a** in the presence of **19** that has been pretreated with Et_2Zn affords alkylation products with *ee* levels similar to those shown in Scheme 2 (76 – 78% *ee*). These data indicate that reactions with Et_2Zn are not promoted by amine ligands that are reduced in situ by various metal hydrides (see ref. [5]).

Concave Butterfly-Shaped Organometallic Hydrocarbons?**

Matthew Laskoski, Gaby Roidl, Mark D. Smith, and Uwe H. F. Bunz*

Carbon-rich organometallic materials are of special interest because their structures display topologies, such as tetragonal or pentagonal, unattainable by their hydrocarbon counterparts.[1–3] In the realm of organic structures, Haley et al. made a series of large polycyclic hydrocarbons of hexagonal topology, in which benzene rings are separated by alkyne units.[4] We are interested in the chemistry and materials science of tetragonal cyclobutadiene complexes,[5] and herein we present the synthesis (**4a** – **c**, see Scheme 1 and 2) and single-



Scheme 1. Synthesis of the unsubstituted bow-tie complex **4a**. a) $[(PPh_3)_2PdCl_2]$, CuI, piperidine, 18 h, 25 °C; aqueous workup and chromatography. b) K_2CO_3, THF, methanol, 16 h, 25 °C. c) $Cu(OAc)_2$, CH_3CN (20 mL), 18 h, 80 °C; aqueous workup and chromatography.

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