Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 6335–6337
Tetrahedron Letters

A promising new catalyst family for enantioselective cycloadditions involving allenes and imines: chiral phosphines with transition metal–CH_2–P: linkages

Alexander Scherer and J. A. Gladysz*

Institut für Organische Chemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Henkestraße 42, 91054 Erlangen, Germany

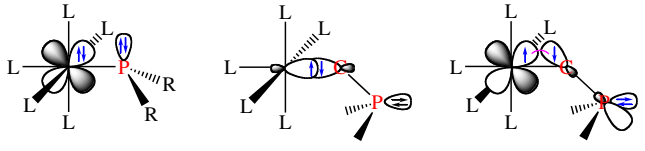
Received 4 July 2006; accepted 5 July 2006
Available online 25 July 2006

Abstract—The racemic rhenium-containing phosphine (η^5-C_5H_5)Re(NO)(PPh_3)(CH_2PPh_3) (**3**) catalyzes the [3+2] cycloaddition of $H_2C{=}C{=}CHCO_2Et$ and *N*-tosyl imines ArCH=NTs in C_6H_6 (RT, 1 d, 20 mol %) to give 2-aryl-3-carbethoxy-3-pyrrolines (Ar=*p*-C_6H_4X (X = H, NO_2, OMe, Me, Cl, Br), 2-furyl; 95–84% isolated). Similar reactions with enantiopure (*S*)-**3** are conducted in C_6H_5Cl at −30 °C (8 d) to maximize enantioselectivities (60–51% ee; 93–90% isolated).

Phosphorus Lewis bases catalyze numerous types of organic transformations, usually via the nucleophilic activation of an educt.[1,2] Most of these reactions are capable of generating new stereocenters. Many chiral phosphorus Lewis bases are now readily available in enantiomerically pure form. Hence, much attention is currently being directed at developing enantioselective versions of these processes.

We wondered whether it might be possible to catalyze such transformations with transition-metal-containing phosphorus Lewis bases of the formulae L_nMPR_2 or $L_nMCH_2PR_2$. Increasing numbers of chiral L_nM fragments are easily accessed in enantiomerically pure form.[3] Furthermore, it is now well established that coordinatively saturated metal fragments enhance the Lewis basicities and nucleophilicities of directly-bound donor atoms D: and CH_2D: analogs.[4–6] This is believed to originate from the types of orbital interactions sketched in Figure 1.[7] Some involve repulsive interactions between filled orbitals (**I**, **IIa**), and others attractive interactions between filled and vacant orbitals (**IIb**). The extensively exploited enhanced nucleophilicities of allyl silanes arise from interactions between Si–C σ and C=C π or π* orbitals analogous to **IIa**,**b**.[8] Accordingly, in this communication we report the first examples of nucleophilic catalysis with $L_nMCH_2PR_2$ species. Appreciable enantioselectivities can furthermore be achieved.

The [3+2] cycloaddition of the allene ethyl 2,3-butadienoate (**1**) and *N*-tosyl imines (**2**), originally developed by Lu, was selected as the test reaction.[9,10] As shown in Scheme 1, this process is catalyzed by Ph_3P and $(n\text{-}Bu)_3P$, and affords chiral functionalized 3-pyrrolines. The first step is believed to generate the zwitterion **III**, to which the tosyl amine adds to give **IV**. For initial screening, the readily available chiral rhenium-containing phosphine (η^5-C_5H_5)Re(NO)(PPh_3)(CH_2PPh_2) (**3**)[11] was chosen. This air-stable eighteen-valence-electron species can be prepared in racemic form in 6 steps and 44% overall yield from commercial $Re_2(CO)_{10}$, or in enantiopure form in 9 steps and 36% overall yield.

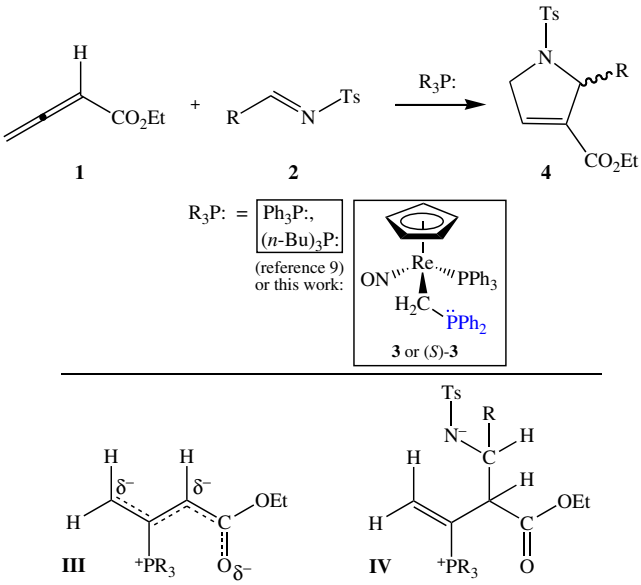


I (metal d lone pair / phosphorus lone pair) **IIa** (σ orbital / phosporus lone pair) **IIb** (metal d lone pair / σ* orbital)

Figure 1. Key orbital interactions in coordinatively saturated L_n MPR_2 (**I**) and $L_nMCH_2PR_2$ (**II**) complexes.

* Corresponding author. Tel.: +49 9131 85 22540; fax: +49 9131 85 26865; e-mail: gladysz@chemie.uni-erlangen.de

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.005



Scheme 1. Phosphine-catalyzed [3+2] cycloadditions of ethyl 2,3-butadienoate (**1**) and *N*-tosyl imines (**2**).

Benzene solutions of **1** and **2** (1.00:1.20 mol ratio) were stirred in the presence of 20 mol % of racemic **3**. After 24 h, flash chromatography gave the aryl-substituted cycloadducts **4a**–**h** as analytically pure powders in 95–84% yields, as summarized in Table 1. Analogous cycloadducts could sometimes be observed with non-aryl substituents. That with R = $C_6H_5CH{=}CH$ (**4i**) was isolated in 61% yield. However, those with aliphatic groups (e.g., *t*-Bu) formed in lower yields, and could not be further purified.

A variety of other conditions were investigated. Comparable yields of **4a** (R = C_6H_5) were obtained in chlorobenzene (93%), $CHCl_3$ (92%), and CH_2Cl_2 (90%). However, temperatures above 40 °C also proved deleterious. NMR spectra of the crude products suggested the presence of a [3+2] cyclodimer of **1** that has been previously isolated from the independent reaction of **1** and PPh_3 (10 mol %) in benzene.[12] Data for **4a**–**i**, most of which are known compounds,[9a] are given in the Supplementary data.

Table 1. Yields and enantioselectivites for cycloadditions (Scheme 1) catalyzed by racemic **3** and (*S*)-**3** (20 mol %)[a]

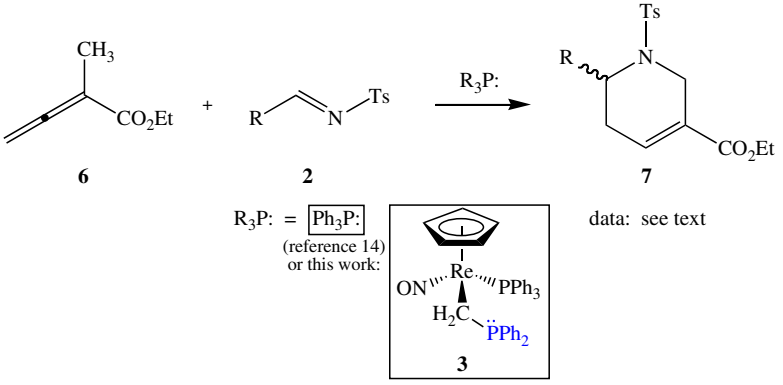
R	Isolated yield (%), racemic **4** (**3**, benzene, RT, 1 d)	Isolated yield (%), scalemic **4** ((*S*)-**3**, chlorobenzene, −20 °C, 8 d)	ee (%) (er)[b], scalemic **4**
a, C_6H_5	94	92	60 (80:20)
b, *p*-$C_6H_4NO_2$	92	90	51 (76:24)
c, *p*-C_6H_4OMe	95	93	54 (77:23)
d, *p*-C_6H_4Me	94	92	58 (79:21)
e, *p*-C_6H_4F	90	90	58 (79:21)
f, *p*-C_6H_4Cl	91	91	52 (76:24)
g, *p*-C_6H_4Br	90	90	57 (79:22)
h, 2-furyl	84	91	56 (78:22)
i, $CH{=}CHC_6H_5$	61	—	—

[a] Benzene, RT (racemic **3**) or chlorobenzene, −20 °C ((*S*)-**3**); see the Supplementary data for additional details.
[b] Determined by HPLC.

Next, similar reactions were examined with (*S*)-**3**. In benzene at room temperature, **1** and **2a** gave **4a** with an ee value of 26%, as assayed by HPLC. In order to maximize enantioselectivities, cycloadditions were conducted in the lower-freezing solvent chlorobenzene at −20 °C. Although longer reaction times were required (8 d), **4a**–**h** could be isolated in 93–90% yields with ee values of 60–51%, as summarized in Table 1.

Complexes with $RePR_2$ linkages are much more nucleophilic than their $ReCH_2PR_2$ analogs.[4,13] Thus, similar reactions of **1** and **2a** were investigated with the phosphido complex (η^5-C_5H_5)Re(NO)(PPh_3)(PPh_2) (**5**).[13] However, no **4a** was detected. Independent reactions of **1a** and **5** showed the rapid formation of allene oligomers, as evidenced by mass spectrometry. Hence, such complexes appear too reactive, presumably giving intermediate zwitterions **III** that are less discriminating than those derived from **3**.

As illustrated in Scheme 2, Kwon has found that the replacement of **1** in Scheme 1 by the methyl-substituted allene $H_2C{=}C{=}C(Me)CO_2Et$ (**6**) leads to tetrahydropyridines **7**.[9d,14] The mechanism involves an alternative C=N addition mode to the zwitterion **III**, followed by proton transfer from the methyl group to nitrogen. Indeed, **3** (20 mol %) could also catalyze this transfor-



Scheme 2. Phosphine-catalyzed [4+2] annulations of ethyl 2-methyl-2,3-butadienoate (**6**) and *N*-tosyl imines (**2**).

mation in benzene at room temperature. However, the yields and purities of the cycloadducts were lower ($R = C_6H_5$, 53%; p-$C_6H_4NO_2$, 47%; p-C_6H_4OMe, 63%), and extended reaction times were required (8 d). The solvents chlorobenzene, $CHCl_3$, and CH_2Cl_2 did not give any improvements. Hence, no enantioselective reactions were attempted.

To our knowledge, there is only one previous study, by Marinetti and Jean, involving non-racemic chiral phosphorus Lewis base catalysts for the cycloadditions in Scheme 1. A number of commercially available enantiopure diphosphines and monophosphines were screened.[10] The systems that gave the highest ee values often afforded only modest yields ((*S*)-BINAP, 45% ee, 13%; (*R*,*R*)-Et-FerroTANE, up to 66% ee, 36%; (*S*)-Phanephos, 64% ee, 32%). The broad and consistent activity that characterizes (*S*)-**3** could not be realized.

Importantly, the rather high loadings of **3** and (*S*)-**3** employed do not reflect any intrinsic problem with catalyst stability or deactivation. Rather, since side reactions dominate above room temperature, the loading represents the only other conveniently-varied parameter for achieving reasonable rates. NMR spectra show that appreciable amounts of catalyst remain when cycloadditions are complete, and the addition of fresh educts gives further reaction. The poorer performance of **3** in Scheme 2 constitutes another manifestation of the often appreciable sensitivity of phosphine catalyzed processes to the reaction conditions, exact nature of the adducts and catalyst, etc.[1] In this context, **3** features a number of diversity elements that can be exploited to optimize yields and selectivities (e.g., the cyclopentadien- yl ligand, the rhenium-bound phosphine, substituents on the spacer carbon or the Lewis basic phosphorus atom that could furthermore introduce new stereocenters).

In summary, **3** and (*S*)-**3** are effective catalysts for the [3+2] cycloaddition in Scheme 1, and allow significant enantioselectivities to be achieved. They represent a promising new direction for transition-metal-containing Lewis bases or 'organocatalysts', nearly all of which have to date been based upon ferrocene, as exemplified by the extensive work of Fu.[15,16] Future reports will describe the use of **3** and (*S*)-**3** as catalysts for other types of organic transformations,[17] as well as advanced-generation catalysts for Schemes 1 and 2.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (DFG, GL 300/8-1; SPP 1179) for support.

Supplementary data

Supplementary data associated with this article (representative procedures, and characterization of **4a–i** (microanalysis, IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry)) can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.005.

References and notes

1. Methot, J. L.; Rousch, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.
2. Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.
3. (a) Brunner, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1194; *Angew. Chem.* **1999**, *111*, 1248; (b) Ganter, C. *Chem. Soc. Rev.* **2003**, *32*, 130.
4. Delacroix, O.; Gladysz, J. A. *Chem. Commun.* **2003**, 665, and earlier references therein.
5. (a) Giner Planas, J.; Hampel, F.; Gladysz, J. A. *Chem. Eur. J.* **2005**, *11*, 1402; (b) Kromm, K.; Eichenseher, S.; Prommesberger, M.; Hampel, F.; Gladysz, J. A. *Eur. J. Inorg. Chem.* **2005**, 298.
6. (a) Fulton, J. R.; Sklenak, S.; Bouwkamp, M. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 4722; (b) Holland, A. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 14684; (c) Fox, D. J.; Bergman, R. G. *Organometallics* **2004**, *23*, 1656; (d) Rais, D.; Bergman, R. G. *Chem. Eur. J.* **2004**, *10*, 3970.
7. For other possible contributing factors, see: Holland, P. L.; Andersen, R. A.; Bergman, R. G. *Comments Inorg. Chem.* **1999**, *21*, 115.
8. Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650.
9. (a) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031; (b) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549; (c) Zhao, G.-L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975; (d) Zhu, X.-F.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276.
10. Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141.
11. (a) Kromm, K.; Zwick, B. D.; Meyer, O.; Hampel, F.; Gladysz, J. A. *Chem. Eur. J.* **2001**, *7*, 2015; (b) Eichenseher, S.; Delacroix, O.; Kromm, K.; Hampel, F.; Gladysz, J. A. *Organometallics* **2005**, *24*, 245.
12. Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.
13. Buhro, W. E.; Zwick, B. D.; Georgiou, S.; Hutchinson, J. P.; Gladysz, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2427.
14. (a) Zhu, Z.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716; (b) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289; (c) Zhao, G.-L.; Shi, M. *Org. Biomol. Chem.* **2005**, *3*, 3686; (d) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234.
15. Fu, G. *Acc. Chem. Res.* **2004**, *37*, 542.
16. For a recent report of a non-ferrocene-based system, see: Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769.
17. Seidel, F.; Gladysz, J. A., in preparation.