ORGANIC LETTERS

2005
Vol. 7, No. 13
2571−2573

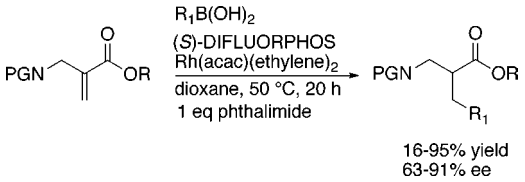
Enantioselective Rhodium Enolate Protonations. A New Methodology for the Synthesis of β^2-Amino Acids

Mukund P. Sibi,* Hiroto Tatamidani, and Kalyani Patil

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105
mukund.sibi@ndsu.edu

Received March 23, 2005

ABSTRACT



Rhodium-catalyzed conjugate addition of an aryl boronic acid to α-methylamino acrylates followed by enantioselective protonation of the oxa-π-allylrhodium intermediate provides access to aryl-substituted β^2-amino acids. The impact of the different variables of the reaction on the levels of enantioselectivity has been assessed.

Rhodium-catalyzed conjugate addition of organoboron,[1] organosilicon,[2] and organotin[3] reagents to α,β-unsaturated systems has seen tremendous advances in the past decade. Hayashi, Miyaura, and others have developed highly efficient enantioselective protocols for these conjugate additions that allows for the establishment of a new chiral center at the β-carbon.[4] In contrast, use of this strategy to establish a stereocenter at the α-carbon has met with limited success.[5] Recently, several examples of enantioselective rhodium enolate protonations leading to enantioenriched α-amino acids and succinates have been reported.[6]

Development of new methods for the synthesis of β-amino acids is important.[7] There are a number of enantioselective methods for the synthesis of β-substituted β-amino acids (β^3-amino acids).[8] In contrast, there are few enantioselective methods for the synthesis of α-substituted β-amino acids (β^2-amino acids).[7] This substitution pattern is of interest since it is present in naturally occurring amino acids as well as compounds with potential therapeutic value.[9]

We have recently developed a novel method for the synthesis of β^2-amino acids using free radical chemistry.[10] The stereochemistry in these reactions was established by an enantioselective H-atom transfer after conjugate radical

(1) (a) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(2) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774.

(3) (a) Oi, S.; Moro, M.; Ono, S.; Inoue, Y. *Chem. Lett.* **1998**, 83. (b) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91.

(4) For recent reviews, see: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(5) For an example of addition to 1-nitrocyclohexene, see: Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

(6) (a) Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719. (b) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083. (c) Chapman, C. J.; Wadsworth, K. J.; Frost, C. G. *J. Organomet. Chem.* **2003**, *680*, 206. (d) Moss, R. J.; Wadsworth, K. J.; Chapman, C. J.; Frost, C. G. *Chem. Commun.* **2004**, 1984. (e) For Co-mediated reduction/protonation: Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 967. Racemic reactions: (f) Chapman, C. J.; Frost, C. G. *Adv. Synth. Catal.* **2003**, *345*, 353. (g) Huang, T.-S.; Li, C.-J. *Org. Lett.* **2001**, *3*, 2037.

(7) For a recent review, see: Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. Also see: Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983.

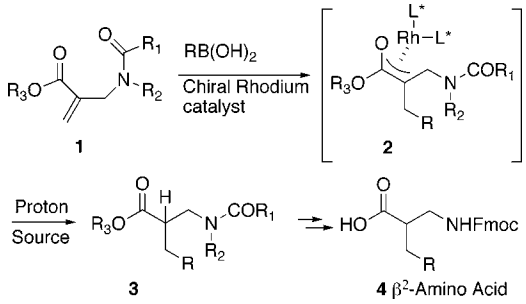
(8) (a) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197. (b) Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 189. (c) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700. (d) Muñoz-Muñiz, O.; Juaristi, E. *Tetrahedron* **2003**, *59*, 4223. (e) Lee, H.-S.; Park, J.-S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575. (f) Seebach, D.; Schaeffer, L.; Gessier, F.; Bindschädler, P.; Jäger, C.; Josien, D.; Kopp, S.; Lelais, G.; Mahajan, Y. R.; Micuch, P.; Sebesta, R.; Schweizer, B. W. *Helv. Chim. Acta* **2003**, *86*, 1852.

(9) Cryptophycins: (a) Subbaraju, G. V.; Golakoti, T.; Patterson, G. M. L.; Moore, R. E. *J. Nat. Prod.* **1997**, *60*, 302. Biologically active β-peptides: (b) Werder, M.; Hauser, H.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1774.

(10) Sibi, M. P.; Patil, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1235.

10.1021/ol050630b CCC: $30.25
Published on Web 05/18/2005

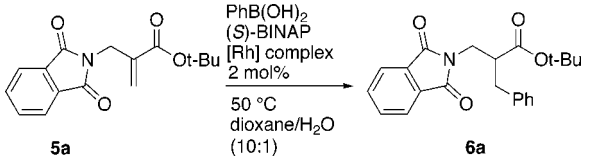
Scheme 1



addition.[11] One deficiency of the H-atom transfer methodology was the inability to incorporate aromatic groups into the targets. We surmised that a rhodium-catalyzed conjugate addition of an aryl boronic acid to **1** followed by enantioselective protonation of the oxa-π-allylrhodium intermediate **2**[1] could provide access to aryl-substituted β^2-amino acids (Scheme 1).[12] Recently, Frost and co-workers have reported a racemic version of the transformation shown in Scheme 1.[13] In this work, we have evaluated several variables for the conversion of **1** to **3**, including the nature of the proton source, chiral ligand, catalyst, nitrogen protecting group, and ester substituent, and report a reasonably efficient method for the synthesis of enantioenriched β^2-amino acids.

Our work began with the identification of an optimal rhodium catalyst for the addition of phenylboronic acid to compound **5a** using BINAP as the chiral ligand and water as the proton source. Our initial choice of catalyst, ligand, and proton source was based on the work of Hayashi,[14] Genet,[6a] Reetz,[6b] and Frost.[6c] Results from these experiments are presented in Table 1. The catalyst rhodium (acac)bisethylene

Table 1. Evaluation of Different Rhodium Complexes[a]

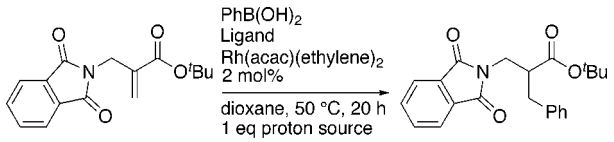


entry	catalyst	yield (SM), %[a]	ee, %[b]
1	$Rh(acac)(ethylene)_2$	76 (0)	41
2	$Rh(OH)(COD)_2$	65 (12)	30
3	$[RhCl(COD)]_2/NaHCO_3$	80 (0)	13
4	$[RhCl(norbornadiene)]_2/NaHCO_3$	76 (2)	25
5	$[RhCl(COD)]_2/AgPF_6$	2 (91)	nd

[a] Isolated yields. Yields in parentheses are for recovered starting materials. [b] Chiral HPLC analysis; nd = not determined.

complex gave a good yield of the addition product with

Table 2. Identification of Optimal Chiral Ligand and Proton Source for the Conversion of **5a** to **6a**



entry	ligand	proton source[a]	yield (SM), %[b]	ee, %[c]
1	(*S*)-BINAP	2-methoxyphenol	31 (49)	81
2	(*S*)-BINAP	2-acetylphenol	84 (2)	77
3	(*S*)-BINAP	phthalimide	56 (34)	82
4	(*S*)-tol-BINAP	2-methoxyphenol	21 (39)	73
5	(*S*)-tol-BINAP	2-acetylphenol	42 (40)	77
6	(*S*,*S*)-DIOP	2-methoxyphenol	43 (31)	36
7	(*R*,*R*)-CHIRAPHOS	2-methoxyphenol	8 (80)	nd
8	(*R*,*S*)-JOSIPHOS	2-methoxyphenol	0 (95)	
9	(*S*)-MethylBOPhoz	2-methoxyphenol	8 (87)	nd
10	(*S*)-SYNPHOS	2-methoxyphenol	1 (73)	nd
11	(*S*)-SYNPHOS	2-acetylphenol	30 (67)	71
12	(*S*)-SYNPHOS	phthalimide	25 (50)	70
13	(*S*)-DIFLUORPHOS	2-methoxyphenol	8 (83)	nd
14	(*S*)-DIFLUORPHOS	2-acetylphenol	71 (15)	88
15	(*S*)-DIFLUORPHOS	phthalimide	91 (0)	88

[a] Performed with 1 equiv of the proton source. The reactions were carried out at 50 °C using dioxane as a solvent and 2 mol % chiral rhodium catalyst. [b] Isolated yields. Yields in parentheses are for recovered starting materials. [c] Chiral HPLC analysis; nd = not determined.

modest enantioselectivity (entry 1). The reactions were effective at 50 °C. Increasing the reaction temperature to 100 °C did not improve the selectivity.[15] Of the four other variants tested, the catalyst derived from rhodium hydroxide (entry 2) and rhodium chloride (entries 3 and 4) gave good yields but only modest selectivity.

With these results at hand, we set out to determine the optimal chiral ligand and proton source for the formation of **6a**. Results from these experiments are presented in Table 2. Several different proton sources have been evaluated by Genet and co-workers in their work on the synthesis of α-amino acids.[6a] In our experiments, three different proton sources and several commercially available phosphine ligands were evaluated.[16] Changing the proton source from water to 2-methoxyphenol led to a decrease in the yield of **6a**. However, there was a large improvement in enantioselectivity (entry 1).[17] This observation is similar to that made by Genet.[6a] The use of 2-acetylphenol as a proton source was very beneficial, providing **6a** in 84% yield and 77% ee (entry

(11) For recent reviews on enantioselective H-atom transfer, see: (a) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. For examples of chiral Lewis acid-mediated H-atom transfer, see: (c) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1293. (d) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984.

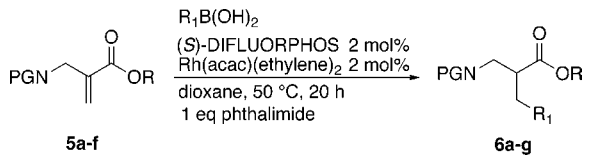
(12) For recent reviews on enantioselective protonations, see: (a) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1. (b) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653. Also see: (c) Muñoz-Muñiz, O.; Juaristi, E. *Tetrahedron Lett.* **2003**, *44*, 2023.

(13) Wadsworth, K. J.; Wood, F. K.; Chapman, C. J.; Frost, C. G. *Synlett* **2004**, 2022. For Heck reactions with α-methylamino acrylates, see: Huck, J.; Receveur, J.-M.; Roumestant, M.-L.; Martinez, J. *Synlett* **2001**, 1467.

(14) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Chirality* **2000**, *12*, 469.

(15) For example, reaction using $Rh(acac)(ethylene)_2$ complex at 100 °C gave the product in 66% yield and 42% ee. We have also observed that prolonged heating of the *tert*-butyl ester at 100 °C leads to decomposition of the starting material.

Table 3. Effect of Nitrogen Protecting Group and Ester Substituent on Selectivity[a]



5a-f 6a-g

entry	nitrogen PG	ester R	R_1	yield (SM), %[a]	ee, %[b]
1	phthalimide	*tert*-butyl **5a**	Ph **6a**	91	88
2	phthalimide	methyl **5b**	Ph **6b**	35 (35)	10
3	phthalimide	cyclohexyl **5c**	Ph **6c**	0	
4	phthalimide	benzyl **5d**	Ph **6d**	85	20
5	succinimide	*tert*-butyl **5e**	Ph **6e**	61	71
6	tosyl	*tert*-butyl **5f**	Ph **6f**	86	81
7	tosyl	*tert*-butyl **5f**	4-BrPh **6g**	23 (67)	84

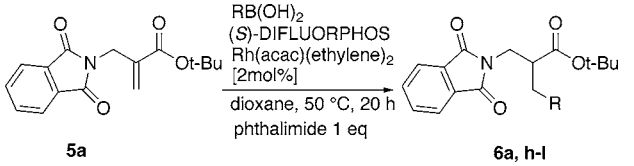
[a] Isolated yields. Yields in parentheses are for recovered starting materials. [b] Chiral HPLC analysis.

2). Phthalimide, with a reasonably acidic N−H, was also functional as a proton source, providing the highest ee for the product with moderate yield (entry 3).[18] The chemical efficiency of the reaction was modest using tol-BINAP as a ligand, but the selectivity was high (entries 4 and 5). Of the several other ligand/proton source combinations tested (entries 6−12), Synphos[19] gave good levels of enantioselectivity (entries 11 and 12). More promising results were obtained using a bisphosphine, DIFLUORPHOS, recently introduced by Genet,[20] as a ligand (entries 13−15). A combination of this ligand and phthalimide as the proton source gave the product in excellent chemical yield and enantioselectivity (entry 15).

Having identified an optimal ligand/proton source combination, we evaluated the effect of the nitrogen protecting group and the ester substituent on efficiency and selectivity (Table 3). These two variables had a significant impact on the course of the reaction. Changing the ester substituent from *tert*-butyl to others with a phthalimido nitrogen protecting group led to either inefficient reactions or low selectivity (entries 1−4). Thus, a bulky ester substituent is essential for obtaining high selectivity. Succinimide and tosyl protecting groups seem promising (entries 5 and 6).

We have preliminarily carried out work on the scope of the aryl boronic acid component in the enantioselective protonation experiments, and these results are shown in Table 4. The reaction conditions which were found to be best for

Table 4. Preparation of Different β^2-Amino Acids



5a 6a, h-l

entry	R	yield (SM), %[a]	ee, %[b]
1	phenyl **6a**	91	88
2	4-chlorophenyl **6h**	71 (10)	84
3	4-methylphenyl **6i**	16 (62)	63
4	4-methoxyphenyl **6j**	84	86
5	3,5-bistrifluoromethylphenyl **6k**	70 (23)	90
6	2-naphthyl **6l**	95	91

[a] Isolated yields. Yields in parentheses are for recovered starting materials. [b] Chiral HPLC analysis.

phenylboronoic acid addition were employed for these studies. In general, the enantioselectivity in these experiments was high (entries 1, 2, and 4−6). However, the chemical yield for the reaction was variable. For example, while reaction with 4-methoxyphenylboronic acid was highly efficient (entry 4), reaction with 4-methylphenylboronic acid gave the product in only 16% yield (entry 3). Of the different substrates evaluated, reaction with 2-naphthylboronic acid gave the highest chemical yield and enantioselectivity (entry 6).

The absolute stereochemistry of the enolate protonation product **6a** derived from reaction with phenylboronic acid and phthalimide as a proton donor was determined to be (*S*)- by converting it into a known compound.[21] A catalytic cycle as postulated by Hayashi and Miyaura[1b] appears to be operative in our experiments also. Genet observed a strong correlation between the level of enantioselectivity and the nature of the proton donor.[6a] A functionality capable of coordinating the rhodium which is located ortho to the proton donor was optimal in their work. In our experiments we suggest that phthalimide containing a carbonyl donor coordinates the rhodium and transfers a proton to the oxa-π-allyl complex. The present work and the prior results in the literature suggest that enantioselective rhodium enolate protonations require a proper matching of all the variables, and development of a general protocol is yet to be achieved.

In conclusion, we have developed a reasonably practical method for the preparation of β^2-amino acids. Furthermore, we have also demonstrated that enantioselective rhodium enolate protonations can be carried out with good selectivity. The extension of the present protocol to more complex susbtrates is underway in our laboratory.

Acknowledgment. We thank the NSF and NIH for financial support of our research programs.

Supporting Information Available: Characterization data for compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050630B

(16) JOSIPHOS = 1-[2-(diphenylphosphino)ferrocenyl]ethyl dicyclohexyl phosphine; MethylBOPhoz = (*R*)-*N*-methyl-*N*-diphenylphosphino-1-[*S*-2-(diphenylphosphino)ferrocenyl]ethylamine; SYNPHOS = [(5,6),-(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine); DIFLUORPHOS = [(4,4′-bi-2,2-difluoro-1,3-benzodioxole)-5,5′diyl]bis(diphenylphosphine).

(17) Product does not racemize under the reaction conditions.

(18) Increasing the amount of phthalimide did not lead to enhancement of the chemical yield or selectivity.

(19) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *PNAS* **2004**, *101*, 5799.

(20) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320.

(21) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 187.