ORGANIC LETTERS
2001
Vol. 3, No. 13
2037−2039

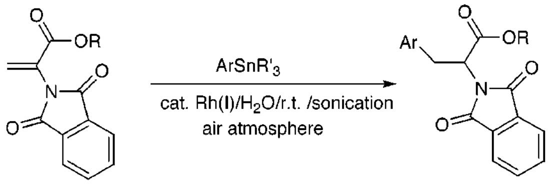
Novel Synthesis of α-Amino Acids via Catalysis in Air and Water

Tai-Sheng Huang and Chao-Jun Li*

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118
cjli@tulane.edu

Received April 19, 2001

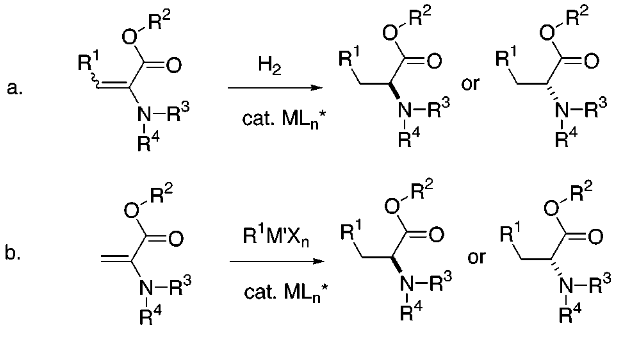
ABSTRACT



A new method was developed for the synthesis of natural and unnatural amino acid derivatives via carbon–carbon bond formation in air and water and at ambient temperature.

Amino acids are the fundamental building blocks of peptides and proteins that play a wide variety of roles in living organisms and display a range of properties.[1] The physiological importance of α-amino acids ensures a sustained interest in their chemistry. Classical methods for the synthesis of α-amino acids, including displacement reactions on α-halo acids, the Strecker synthesis, via hydantoins, and via oxazolones have played key roles in the early days of amino acid chemistry.[2] Among the many recent methods developed for the synthesis of α-amino acids are the Petasis boronic acid method,[3] the Alper double carbonylation method,[4] Lewis acid catalyzed imine additions,[5] and (above all) the catalytic hydrogenation of amino acrylates.[6,7] Recently, extraordinary progress has been made in the chemical synthesis of α-amino acids via asymmetric catalytic hydrogenation of acetamidoacrylates, mostly with rhodium (as well as ruthenium, iridium and copper) catalysts (Figure 1, route a). A large numbers of chiral ligands have also been developed for such a purpose.[8] On the other hand, a complimentary synthesis via carbon−carbon bond formation (Scheme 1, route b) has been rarely explored. Herein, we wish to describe a novel synthesis of α-amino acids via rhodium-catalyzed conjugated addition of α-aminoacrylates with organotin[9] and organobismuth reagents under ambient conditions of air and water.

Scheme 1



Currently, there is a wide interest in searching for alternative media and processes for chemical and organic synthesis.[10] As a result of the natural abundance of water as

---

[1] *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Eds.; Chapman & Hall: London 1985.

[2] Williams, R. M. In *Organic Chemistry Series, Volume 7: Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, 1989. Duthaler, O. R. *Tetrahedron* **1994**, *50*, 1539. Kunz, H. In *Stereoselective Synthesis*; Helmechen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Theime Verlag: Stuttgart, 1995; Vol. E21b, p 1931; Whitesell, J. K. *Acc. Chem. Res*. **1985**, *18*, 280 and references therein.

[3] Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1997**, *119*, 445. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1998**, *120*, 11798.

[4] Li, Y. S.; Alper, H. *Angew. Chem., Int. Ed*. **2001**, *40*, 779.

[5] O'Donnell, M. J.; Bennett, W. D. *Tetrahedron* **1988**, *44*, 5489.

[6] Burk, M. J. *Chemtracts: Org. Chem*. **1998**, *11*, 787.

[7] Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711.

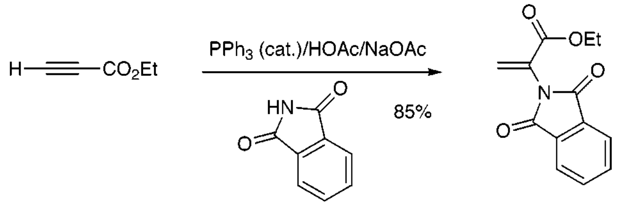
[8] For latest examples, see: Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed*. **2000**, *39*, 3889. van den Berg, M.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc*. **2000**, *122*, 11539.

10.1021/ol010079s CCC: $20.00

well as the inherent advantages of using water as a solvent, interest has been growing in studying organic reactions in water.[11] Recently, we have been exploring transition-metal-catalyzed carbon−carbon bond formations under the quasi-natural conditions of air and water.[12] Toward such a general goal, we recently discovered a Grignard-type phenylation of aldehydes in water. Phenyltin derivatives (trimethyl and tributyl) reacted effectively with aldehydes in water and under an atmosphere of air to give nucleophilic addition products in high yields in the presence of a catalytic amount of rhodium catalyst.[13] Subsequently, we also found that in the presence of a rhodium catalyst, α,*β*-unsaturated esters and ketones react with triphenylbismuth as well as trialkylphenyl- and trialkylvinyltin reagents in aqueous media to give the corresponding conjugated addition products under an air atmosphere.[14] While the processes are open for further improvements, the effectiveness of such reactions led us to explore the synthesis of amino acids under similar conditions. Previously, the conjugated addition of acetamidoacrylates with organocuprate reagents have been briefly studied under inert gas atmosphere and in anhydrous solvent.[15]

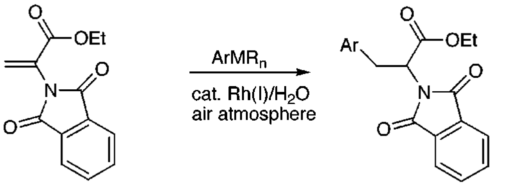
Electron-deficient α-phthalimidoacrylate derivatives were chosen because of their stability in water and their enhanced reactivity toward nucleophiles. There are a number of methods in the literature for forming acetamidoacrylates and related compounds.[16] However, we found that the most convenient method was via the Trost α-addition reaction of acetylenic carboxylic derivatives catalyzed by triphenylphosphine in toluene.[17] Thus, the reaction of ethyl propynoate with phthalamide in toluene under Trost reaction conditions generated the desired ethyl α-phthalimidoacrylate in 85% yield (Scheme 2).

Scheme 2



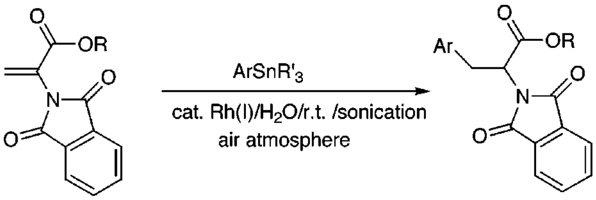
With the aminoacrylate derivative in hand, we examined the conditions for conjugated addition. When ethyl α-phthalimidoacrylate was stirred with triphenylbismuth and a catalytic amount of a $Rh_2(COD)_2Cl_2$ (5 mol %) at refluxing conditions overnight in water, a smooth reaction occurred to give the conjugated product in 72% isolated yield. No reaction was observed without the catalyst. However, at a low temperature (<70 °C), the bismuth compound became a solid and only 45% of the desired product was obtained after 2 h of sonication, which limited its reaction. When trimethylphenyltin was used instead of the bismuth compound, only 18% yield of the desired product was isolated after refluxing overnight; most of the starting material had decomposed. When the mixture was stirred at room temperature (to prevent the decomposition), no reaction was observed (Scheme 3). However, when the reaction mixture in water was sonicated[18] at room temperature, a fast reaction occurred to give the desired product in 82% isolated yield. Interestingly, only 11% yield of the desired product was obtained when the reaction mixture was sonicated in dioxane. Various tin reagents were then examined under the same reactions conditions of sonication in air and water (Scheme 4), and the results are listed in Table 1. Replacing trimethyltin with tributylphenyltin (in general) decreased the yield of the product slightly (compare entries 1 and 2, 4 and 5). Whereas an electron-withdrawing group on the phenyl ring decreased the yield (entries 3 and 4), no major change was observed with electron-donating groups.

Scheme 3



$ArMR_n$	conditions	yield (%)
Ph_3Bi	H_2O/reflux/overnight	72
Ph_3Bi	H_2O/r.t./sonication/2h	45
$PhSnMe_3$	H_2O/reflux/overnight	18
$PhSnMe_3$	H_2O/r.t./overnight	0
$PhSnMe_3$	H_2O/r.t./sonication/2h	82
$PhSnMe_3$	dioxane/r.t./sonication/2h	11

Scheme 4



---

(9) Qi, S.; Moro, M.; Ono, S.; Inoue, Y. *Chem. Lett.* **1998**, 83; Qi, S.; Moro, M.; Inoue, Y. *Chem. Commun.* **1997**, 1621.

(10) Caution: trimethyltin reagents are highly toxic. For general references on green chemistry, see: Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998. *Green Chemistry: Designing Chemistry for the Environment*; ACS Symposium Series No. 626; Anastas, P. T., Williamson, T. C., Eds.; American Chemical Society: Washington, DC, 1996.

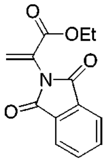
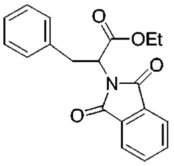
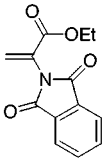
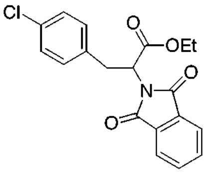
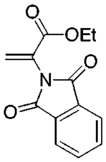
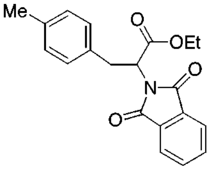
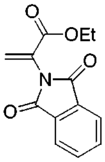
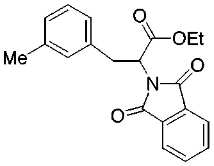
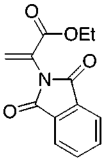
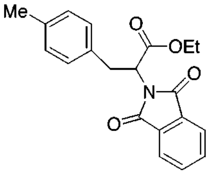
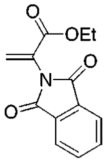
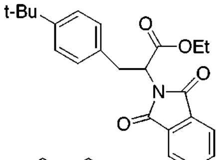
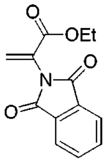
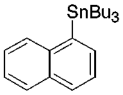
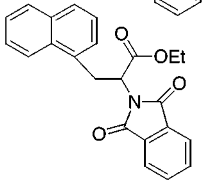
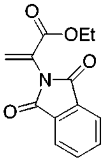
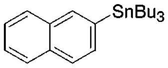
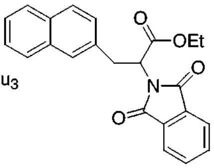
(11) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: Glasgow, 1998.

(12) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. Li, C. J. *Tetrahedron* **1996**, *52*, 5643.

(13) Meng, Y.; Li, C. J. *J. Am. Chem. Soc.* **2000**, *120*, 9538.

(14) Venkatraman, S.; Li, C. J. *Tetrahedron Lett.* **2001**, *42*, 781. For other Rh-catalyzed conjugated additions, see: Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716 and references therein.

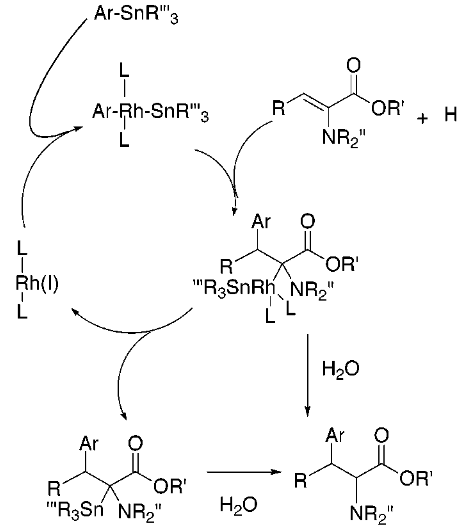
Table 1. Synthesis of α-Amino Acid Derivatives via Rhodium-Catalyzed Conjugated Additions in Air and Water[a]

entry	enamide	stannane	product	yield (%)
1		$PhSnBu_3$		57
2		$PhSnMe_3$		82
3		*p*-$ClPhSnBu_3$		41
4		*p*-$ClPhSnMe_3$		32
5		*p*-$MePhSnMe_3$		76
6		*m*-$MePhSnMe_3$		71
7		*p*-$MeOPhSnMe_3$		70
8		*t*-$BuPhSnMe_3$		61
9				51
10				76

[a] All reactions were carried out at room temperature. Isolated yields are after column chromatography on silica gel.

A tentative mechanism for the reaction involves the insertion of rhodium in the aryl C−M bond to generate a rhodium intermediate. The intermediate undergoes conjugated addition with acrylate derivatives to give a α-rhodium carbonyl intermediate. Either direct hydrolysis of this intermediate or a reductive elimination followed by hydrolysis of the α-tin carbonyl intermediate will result in the final product (Scheme 5).

Scheme 5. Tentative Mechanism for the Rhodium-Catalyzed Synthesis of Amino Acids



In summary, a method for the synthesis of natural and unnatural α-amino acid derivatives was developed in air and water. The scope (such as asymmetric synthesis), mechanism, and synthetic applications of this reaction are currently under investigation.[19]

Acknowledgment. We are grateful to the NSF (CAREER), the NSF-EPA joint program for a sustainable environment, and the Louisiana Board of Regent for partial support of our research.

Supporting Information Available: Characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010079S

---

(15) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Naso, F.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 4387. Blanchard, P.; El Kortbi, M. S.; Fourrey, J. L.; Robert-Gero, M. *Tetrahedron Lett.* **1992**, *33*, 3319. Bull, S. D.; Davis, S. G.; O'Shea, M. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3657.

(16) Ffenberger, F.; Beissenger, T. *Angew. Chem.* **1982**, *94*, 210. Wojciechowska, H.; Pawlowicz, R.; Andruszkiewicz, R.; Grzybowska, J. *Tetrahedron Lett.* **1978**, 4063. Carlstroem, A. S.; Fred, T. *Synthesis* **1989**, 414.

(17) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.

(18) Cintas, P.; Luche, J.-L. *Green Chem.* **1999**, *1*, 115. *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum: New York, 1998. Ganem, B. *Chemtracts: Org. Chem.* **1990**, *3*, 438. Ley, S. V.; Low, C. M. R. *Ultrasound in Synthesis*; Springer-Verlag: New York, 1989.

(19) **Typical Procedure.** A suspension of ethyl α-phthalimidoacrylate (61 mg, 0.25 mmol), trimethyl(phenyl)tin (120 mg, 0.5 mmol), and chloro-(1,5-cyclooctadiene)rhodium(I) dimer (6 mg, 0.0125 mmol) in 3 mL of water was sonicated for 2 h in a commercial ultrasonic cleaning bath at room temperature. After the reaction was complete (as monitored by TLC), 15 mL of ethyl acetate was added. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (eluent, hexane/ethyl acetate, 4:1) to give the desired product (62 mg, 82%).