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Controlling Olefin Geometry with Pd Catalysis: Selective Formation of *Z*-olefins from Both *E*- and *Z*-Allylic Carbonates

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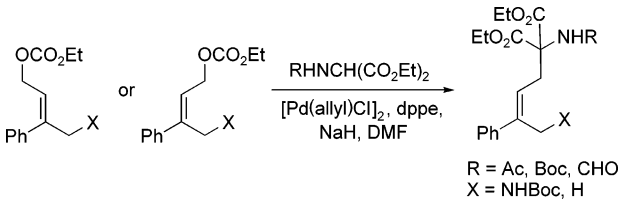
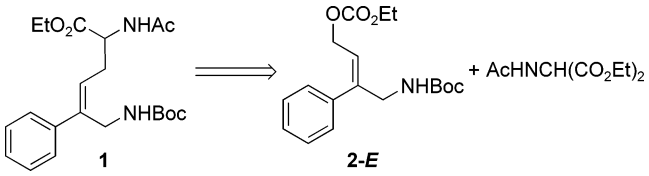


The palladium-catalyzed formation of *Z*-olefins from allylic carbonates and a variety of protected dialkyl aminomalonates is reported. The reaction is selective for the *Z*-isomer, and either acetyl, Boc, or formyl protecting groups are tolerated. The *Z*-olefin product can be formed regardless of whether the *E*- or *Z*-allylic carbonate is used as starting material.

The placement of synthetic amino acids in peptides is one of the most straightforward techniques to potentially enhance peptide stability and increase receptor affinity.[1] Synthetic amino acids are frequently used by medicinal chemists as a key component in establishing and optimizing structure activity relationships due to their effects on receptor selectivity and binding. As a consequence, the development of efficient and cost-effective methods for the selective preparation of substituted synthetic amino acids continues to attract attention.[2]

The allylation of glycine derivatives represents one of the most direct approaches for the preparation of synthetic amino acids due to the versatility of the products.[3] Toward this end, dialkyl aminomalonates, benzophenone imine, and azalactone derivatives of glycine have been successfully employed as nucleophiles in palladium-catalyzed allylic alkylation reactions.[4,5] We were recently faced with the challenge of preparing olefin **1** as a single geometric isomer. The palladium-catalyzed allylic alkylation of carbonate **2** with a glycine equivalent such as diethyl *N*-acetamidomalonate would represent a straightforward route to **1** if the regiochemistry and olefin geometry could be controlled (Scheme 1).

SCHEME 1



We were particularly interested in using diethyl *N*-acetamidomalonate as a glycine surrogate, since it is inexpensive and readily available and can be converted to an amino ester or amino acid via straightforward decarboxylation procedure. In addition, the presence of a robust acetamide protecting group allows for a high degree of product elaboration without the concern of unwanted deprotection. A survey of the literature reveals that most examples of the palladium-catalyzed alkylation reaction are reported with 1,2-disubstituted olefins. Allylic substitution reactions with unsymmetrical 1,1-disubstituted olefins are less common.[6] This is perhaps not surprising, given the reaction's degree of complexity, since with these substrates one must control both the regiochemistry of the addition reaction and the olefin geometry of the product. In this publication, we report the highly selective palladium-catalyzed allylation of a variety of 1,1-disubstituted allylic carbonates with substituted dialkylaminomalonate derivatives to afford the *Z*-olefin product.

Preparation of allylic alkylation substrate **2-*E*** was accomplished in 57% overall yield via DIBAL-H reduction of the previously reported, readily accessible trisubstituted unsaturated ester, followed by treatment with ethyl chloroformate and pyridine.[7] We were pleased to find that subjecting **2-*E*** to 2.5 mol % $[allylPdCl]_2$, 10 mol % 1,2-bis(diphenylphosphino)ethane (dppe), diethyl *N*-acetamidomalonate, and NaH as base in DMF at 90 °C for 12 h afforded a mixture of the allylation products **3-*Z***:**3-*E*** in a 13:1 ratio. Assay yield of the product was ~80%,

(1) Krohn, K.; Kirst, H.; Maag, H. *Antibiotics and Antiviral Compounds*; VCH: Weinheim, 1993. Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726−731.

(2) Smith, A. B., III; Guzman, M. C.; Sprengler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carrol, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947−9962.

(3) (a) Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1993**, *34*, 4485−4488. (b) Kopola, N.; Friess, B.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1989**, *30*, 3963−3966.

(4) For a general review, see: (a) Trost, B. N.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (b) Ito, Y.; Kuwano, R. *J. Am. Chem. Soc.* **1999**, *121*, 3236−3237. (c) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1468−1470. (d) Kuwana, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104−12105. (e) Kuwana, R.; Kondo, Y. *Org. Lett.* **2004**, *6*, 3545−3547. (f) Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Terahedron Lett.* **1990**, *31*, 5049−5052. (g) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2814−2816. (h) Bayardon, J.; Sinou, D. *J. Org. Chem.* **2004**, *69*, 3121−3128. (i) For a Ru-catalyzed example, see: Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2003**, *41*, 6.

(5) (a) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329−3331. (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Am. Chem. Soc.* **2002**,*67*, 7418−7428. (c) Stolle, A.; Olivier, J.; Piras, P. P.; Salaun, J.; de Meijere, A. *J. Am. Chem. Soc.* **1992**, *114*, 4051−4067. (d) Genet, J. P.; Juge, S.; Achi, S.; Mallart, S.; Montes, R. J.; Levif, G. *Tetrahedron* **1988**, *44*, 5263−5276. (e) Cazes, B.; Gore, J. *J. Chem. Res.* **1996**, *11*, 2768−2792.

(6) (a) Trost, B. M.; Heinemann, C.; Ariza, X.; Weigand, S. *J. Am. Chem. Soc.* **1999**, *121*, 8667−8668. (b) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727−10737. (c) Hou, X.-E.; Sun, N. *Org. Lett.* **2004**, *6*, 4399−4401. (d) Tamaru, Y.; Horino, Y.; Araki, M.; Tanak, S.; Kimura, M. *Tetrahedron Lett.* **2000**, *41*, 5705−5709. (e) Commandeur C.; Thorimbert, S.; Malacria, M. *J. Org. Chem.* **2003**, *68*, 5588−5592. (f) Gamez, P.; Ariente, C.; Gore, J.; Cazes, B. *Tetrahedron* **1998**, *54*, 14835−14844. (g) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575−2578. (h) Takano, D.; Nagamitsu, T.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Kuwajima, I.; Omura, S. *Org. Lett.* **2001**, *3*, 2289−2291.

(7) Baxter, J. M.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215−218. All allylic carbonates utilized in this work are single isomers by HPLC.

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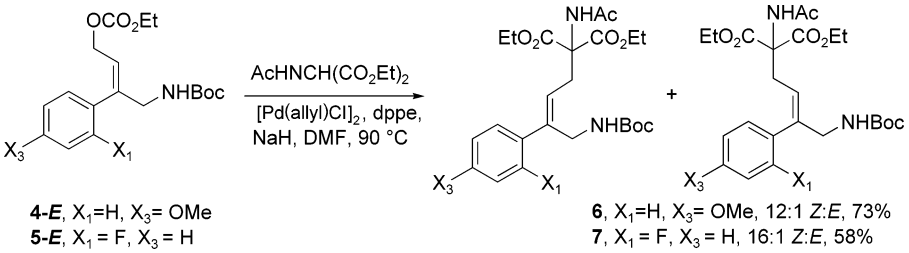
SCHEME 2



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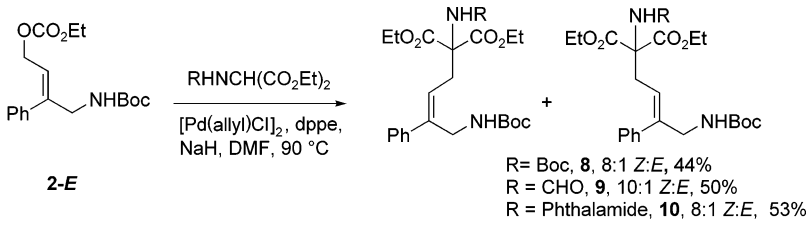

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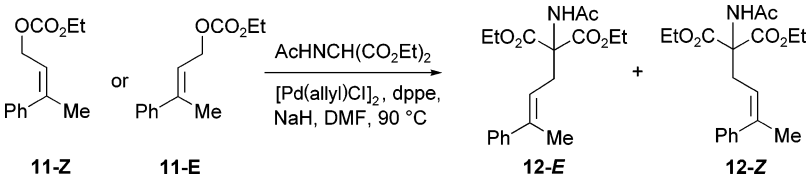
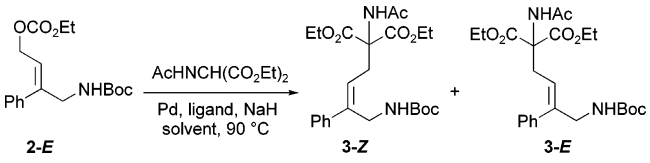


TABLE 1. Screening of Catalysts and Solvents with 2-*E*



entry	Pd source[a]	ligand[b]	solvent[c]	*Z*:*E* ratio[d]	conv (%)[d]
1	[allylPdCl]$_2$	dppe	DMF	13:1	98
2	[allylPdCl]$_2$	dppe	THF	2:1	96
3	[allylPdCl]$_2$	binap	THF	1:2	95
4	[allylPdCl]$_2$	dppp	DMF	3:1	99
5	[allylPdCl]$_2$	dppb	DMF	3:1	99
6	[allylPdCl]$_2$	binap	DMF	1:2	97
7	[allylPdCl]$_2$	Ph_3P	DMF	4:1	96
8	Pd_2dba_3	dppe	DMF	3:1	20

[a] 2.5 mol% of Pd catalyst. [b] 10 mol% of bidentate phosphine, 20 mol % Ph_3P. [c] Reactions in THF were run at 40 °C (entry 2) or 50 °C (entry 3) for 12 h. Reactions in DMF were run at 90 °C for 12 h, except for entry 6, which was complete in 3 h. [d] *Z*:*E* ratios and conversion determined by HPLC and NMR analysis of crude reaction mixture.

and the major olefin product **3-*Z*** was isolated in 52% yield. The identity of the *E*-olefin product was confirmed by independent synthesis, and the olefin geometries of both products were confirmed by NOE experiments.[8]

A brief survey of reaction parameters was performed to determine the optimal reaction conditions (Table 1). Use of THF as solvent, in place of DMF, gave only a 2:1 *Z*:*E* product ratio. Substitution of [allylPdCl]$_2$ with Pd_2dba_3 resulted in only 20% conversion. Use of 1,3-bis(diphenylphosphino)propane (dppp), 1,4-bis(diphenylphosphino)butane (dppb), or Ph_3P as ligand resulted in lower selectivity for the *Z* isomer, 2:1 to 4:1 *Z*:*E* ratios. Interestingly, binap reverses the selectivity in favor of the *E* isomer, 2:1.

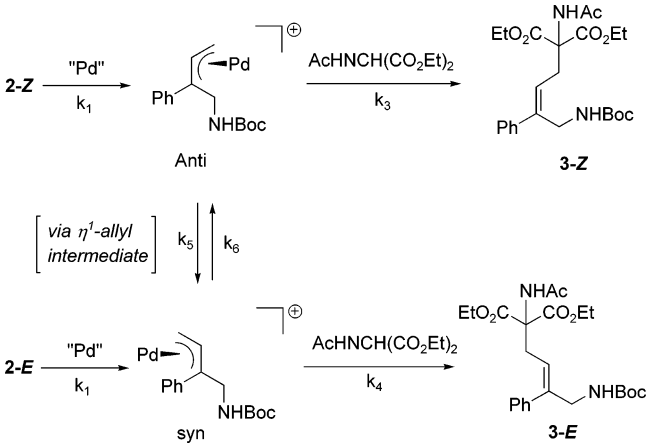
We next investigated the influence of the electronic characteristics of the aryl ring on the allylation reaction (Scheme 2). Use of the *p*-MeO ethyl carbonate **4-*E*** under our optimized conditions afforded a 12:1 ratio of *Z*:*E* olefin products. The pure **6-*Z*** isomer was isolated in 73% yield. The *o*-F ethyl carbonate **5-*E*** afforded a 16:1 mixture of isomers, and the pure isomer **7-*Z*** was isolated in 58% yield. Both of these results support the conclusion that electronic factors have minimal influence on product selectivity.

The scope of the reaction was examined by surveying other substituted aminomalonate nucleophiles (Scheme 3). Allylic alkylation of **2-*E*** using diethyl *N*-Boc aminomalonate gave a 8:1 *Z*:*E* product ratio, and the pure **8-*Z*** isomer was isolated in 44% yield, whereas the use of diethyl *N*-formamidomalonate gave a 10:1 *Z*:*E* product ratio and a 50% isolated yield of **9-*Z***. Reaction of the phthalamide-protected diethyl amino-malonate with carbonate **2-*E*** afforded 8:1 *Z*:*E* product selectivity, and a 53% isolated yield of **10-*Z*** was obtained.

A straightforward rationale for the observed selectivity of these reactions is to invoke chelation of the *N*-Boc carbonyl group at the palladium π-allyl intermediate prior to nucleophilic attack. To probe the effect of the NHBoc group on the selectivity, both **11-*Z*** and **11-*E*** allylic carbonates were prepared and subjected to the optimized reaction conditions. Both reactions afforded the *E*-product, but the selectivity using **11-*E*** was 40:1 *E*:*Z* whereas **11-*Z*** afforded a 18:1 *E*:*Z* ratio (Scheme 4). The high selectivity observed in the absence of the NH-Boc suggests that coordination of this group to the Pd is not the governing factor controlling product selectivity. These results are similar to the selectivity that was observed by Trost et al. in the allylic alkylation of tertiary allylic acetates with tertiary azalactone nucleophiles.[6]

(8) See Supporting Information for the synthesis of all starting material, products, and all NMR data.

SCHEME 5



The effect of the olefin geometry of the starting material on the *Z*:*E* selectivity of the alkylation reaction was also investigated. Subjecting ethyl carbonate **2-*Z*** to the standard reaction conditions gave a 24:1 *Z*:*E* product selectivity. Running this same reaction in THF at 45 °C improved the **3-*Z*: 3-*E*** ratio to 40:1. These results are consistent with the solvent screening results in Table 1, which suggests that the rate of isomerization of the palladium π-allyl intermediate is slower in THF.

This result along with the results described above can be rationalized using the mechanistic scheme shown in Scheme 5. While conversion of **2-*Z*** to **3-*Z*** is mechanistically straightforward, conversion of **2-*E*** to **3-*Z*** requires isomerization of the palladium π-allyl complex via an η^1-intermediate prior to alkylation. Furthermore, the slight difference in product ratios of **3-*Z*** and **3-*E*** from **2-*E*** and ***2*-*Z*** suggests that the reaction is not under Curtin−Hammett control. Using 2 equiv of the nucleophile under the standard reaction conditions decreased the selectivity to 4:1 *Z*:*E*, suggesting that the rate of isomerization is competitive with the rate of alkylation. Further mechanistic investigations will be required to address these issues.

In conclusion, we report a selective and practical method for the formation of a variety of functionalized *Z*-allylated glycine products from *E*-allylic carbonates. The stereodefined allylic carbonate starting material can be easily prepared from *N*-Boc glycine in five high-yielding steps. Based on these results, we anticipate more examples of palladium-catalyzed allylation reactions with unsymmetrical 1,1-disubstituted olefins will be reported in the future.

Experimental Procedure

General Procedure for Preparation of Allylic Carbonates. To a −78 °C solution of the unsaturated ester (31.0 mmol) in 100 mL of CH_2Cl_2 was added DIBAL-H (71 mmol, 47 mL of 1.5 M in toluene). After stirring for 1 h at −78 °C, the reaction was complete, 90 mL of a 20 wt % aqueous solution of $NaHSO_4$ was slowly added, and the solution was warmed to ambient temperature. The solution was diluted with 90 mL of isopropyl acetate, and the aqueous layer was cut away. The organic layer was washed with 90 mL of brine and concentrated. The residue was either purified by chromatography with hexane/EtOAc or crystallization from heptane/isopropyl acetate. The compounds were used directly in the next step. The allylic alcohol (15.2 mmol) in 40 mL of CH_2Cl_2 was treated with pyridine (17.7 mmol, 1.8 mL) and ethyl chloroformate (16.7 mmol, 1.8 mL) at 10 °C. After stirring for 4 h the solution was diluted with 40 mL of isopropyl acetate, and 20 mL of H_2O was added. After the phase cut, the organic layer was washed with 2 × 30 mL of 1.0 N HCl and 2 × 30 mL of brine and dried over $MgSO_4$. Concentration and chromatography on silica gel with hexanes/ethyl acetate afforded the product.

General Procedure for Pd-Catalyzed Allylic Substitution Reaction. A Schlenk flask was charged with the amino malonate nucleophile (1.8 mmol) and 3 mL of DMF. Under a stream of nitrogen, NaH (1.8 mmol, 60 wt % suspension) was added, and the solution aged for 10 min. Under a stream of nitrogen, 1,2-bis(diphenylphosphino)ethane (0.17 mmol), $[allylPdCl]_2$ (0.04 mmol) and the allylic carbonate (1.67 mmol) in 3 mL of DMF were added in that order. The flask was evacuated and backfilled with N_2 three times. The resulting reaction was stirred overnight at 90 °C under N_2. HPLC of the reaction mixture indicated complete conversion. The mixture was cooled to room temperature, and 10 mL of isopropyl acetate was added followed by 5 mL of water. After the phase cut, the aqueous layer was extracted with 2 × 10 mL of isopropyl acetate. The organic layers were washed with 2 × 10 mL of 1.0 N NaOH, 2 × 10 mL of 1.0 N HCl, and 3 × 10 mL of brine. The organic layer was dried over $MgSO_4$, and then evaporation and chromatography on silica gel with the indicated solvent system afforded the product.

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

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