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Hydrogen-Bond-Directed Highly Stereoselective Synthesis of Z-Enamides via Pd-Catalyzed Oxidative Amidation of Conjugated Olefins

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Abstract: An efficient procedure for the preparation of *Z*-enamides has been developed, involving the reaction of primary amides with conjugated olefins using a Pd/Cu cocatalyst system. It was found that certain additives, such as phosphine oxides and phosphonates, increase the efficiency of the reaction in nonpolar solvents under an oxygen atmosphere, thus producing a variety of *Z*-enamides in high yields with excellent stereoselectivity under Wacker-type conditions. The oxidative amidation reaction has a broad substrate scope, allowing alkyl, aryl, and vinyl amides to react with olefins conjugated with ester, amide, phosphonate, and ketone groups. The notable preference for the formation of *Z*-enamides is presumably due to the presence of an intramolecular hydrogen bond between the amido proton and the carbonyl oxygen. The energy difference between two plausible σ-alkylamidopalladium intermediates, leading to *Z*- and *E*-isomeric enamide products, respectively, was calculated to be 4.18 kcal/mol. The β-hydride elimination step is assumed to be a stereochemistry-determining step in the overall oxidative amidation process, with the energy level for the transition state leading to the *Z*-enamide being 5.35 kcal/mol lower than that leading to the *E*-isomer. The efficiency of photoisomerization between *Z*- and *E*-enamides was observed to be largely dependent on the substrates' substituents, and certain *E*-enamides could be obtained in synthetically useful yields by photoirradiation of *Z*-isomers. Synthetic application of the present method was successfully demonstrated by a direct formal synthesis of *cis*-CJ-15,801.

Introduction

Hydrogen bonds serve as one of the most essential motifs both in molecular recognition and for defined organization of important molecules in chemistry and biology.[1] Although numerous examples of hydrogen-bonding-driven approaches have been reported in crystal engineering and self-assembly,[2] the use of this noncovalent interaction in catalysis has been less frequently investigated. In fact, only in recent years have hydrogen bonds been utilized as a key feature to control activity and/or selectivity in certain catalytic transformations,[3] such as Diels−Alder, epoxidation, aldol, Michael, hydrogenation, and cycloaddition reactions.[4]

Enamides are widely present as a key structural moiety in numerous natural products,[5] such as palytoxin,[6a] terpeptin,[6b] aspergillamides,[6c] chondriamides,[6d] salicylihalamides,[6e] apicularen A,[6f] TMC-95A-D,[6g] crocacins,[6h] lansiumamide A,[6i] storniamides,[6j] and enamidoin.[6k] In addition, enamides serve as highly versatile synthetic intermediates, especially in the formation of heterocycles and in asymmetric synthesis for the generation of secondary or tertiary chiral amines.[7] As a result, several protocols have been devised for the preparation of

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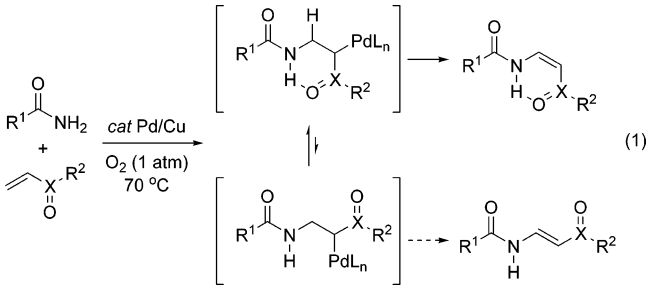
enamides. Conventional approaches include addition of amides to alkynes,[8] condensation of ketones or aldehydes with amides,[9] elimination of alcohols from *N*-(α-alkoxyalkyl)amides,[10] dehydration of hemiaminal,[11] acylation of imines,[12] Curtius rearrangement of α,β-unsaturated acyl azides,[13] and elimination of β-hydroxy-α-silylamides (Peterson reaction).[14]

On the other hand, several catalytic routes have been also investigated, such as isomerization of *N*-allylamides by Fe, Rh, or Ru complexes[15] and Rh-catalyzed β-hydride elimination of diazoamides.[16] Additionally, metal-mediated C−N bond formation has been an area of great interest, and some protocols have been developed, including Ru- or Cu-catalyzed addition of amides to alkynes[17] and coupling of vinyl (pseudo)halides with amides using Pd[18] or Cu species.[19] Despite the numerous examples for the catalytic synthesis of enamides, such reactions often suffer from either low yield or difficulty in preparing necessary vinyl halides. More importantly, stereocontrol of the double bond presents an additional challenge, particularly when *Z*-enamides are required.[20−23] This is especially noteworthy, considering that significant progress has been made recently in direct oxidative amination of olefins with simple amines.[24] For example, Hirai et al. previously reported an amidation protocol using a stoichiometric palladium complex.[25] Murahashi and coworkers later demonstrated that enamides could be readily obtained by the reaction of amides or carbamates with olefins using Pd and Cu cocatalysts under an oxygen atmosphere.[26] However, reaction of lactams or cyclic carbamates afforded predominantly *E*-enamides, whereas a mixture of isomeric enamides was obtained with acyclic amides. More recently, Stahl et al. have contributed to a significant advance by expanding the scope of the nucleophiles, including oxazolidinone, phthalimide, secondary amide, and sulfonamide, in amination of simple olefins via either Markovnikov or *anti*-Markovnikov manner by the choice of catalyst system, although the requirement for excess amounts of certain types of olefins and low product yields in some cases leave room for further improvements.[27,28]

Despite the recent progress, there are still several issues to be addressed, such as substrate scope, stereoselectivity, and mildness of reaction conditions for the efficient preparation of enamides. Therefore, *direct oxidative amidation of alkenes instead of vinyl halides would be highly desirable, especially if it yields high stereoselectivity in the formation of enamides under mild conditions*. In this article, we reveal our studies on the development of such a straightforward method for producing *Z*-enamides with high stereoselectivity through a hydrogen-bond-directed approach (eq 1).[29]



(1)

Results and Discussion

At the outset of our studies on the oxidative amidation reaction, benzamide (**1**) and ethyl acrylate (**2**) were chosen as model substrates, and various reaction conditions were subsequently examined (Table 1). We were especially interested in

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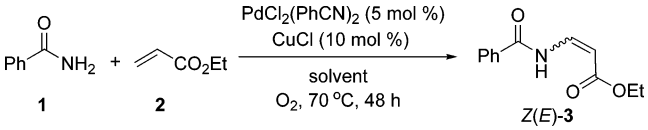
Table 1. Optimization of the Reaction Conditions in the Oxidative Amidation[a]



entry	solvent	conv (yield, %)[b]	Z/E[c]
1	DMF	<5 (0)	
2	DMSO	<5 (0)	
3	DME	91 (86)	2.4:1
4	THF	78 (67)	3.0:1
5	dioxane	83 (60)	4.8:1
6	1,2-dichloroethane	50 (34)	>30:1
7	toluene	65 (37)	>30:1
8	chlorobenzene	56 (47)	>30:1
9	chlorobenzene (w/o Cu)	10 (<5)	
10[d]	chlorobenzene	7 (<5)	
11[e]	chlorobenzene	46 (41)	>30:1
12	chlorobenzene (N_2)	8 (<5)	

[a] Reaction conditions: a mixture of benzamide (1 equiv), ethyl acrylate (3.0 equiv), $PdCl_2(PhCN)_2$ (5.0 mol %), and CuCl (10 mol %) in the indicated solvent (0.2 M) was stirred at 70 °C for 48 h under 1 atm of O_2. [b] Determined by ^1H NMR using an internal standard (anisole) and combined isolated yields of both isomers. [c] Isomeric ratio of crude reaction mixture determined by ^1H NMR. [d] $CuCl_2$ (10 mol %) was used instead of CuCl. [e] Benzoquinone (1.0 equiv) was used instead of CuCl.

applying Wacker-type reaction conditions[30] because it was envisioned that the protocol would eventually be amenable to a practical process. It was observed that solvent polarity has a dramatic effect on the efficiency as well as selectivity in the conversion. For example, when the reaction was carried out in DMF or DMSO, it was quite sluggish and a negligible conversion was observed after 48 h using a Pd/Cu cocatalyst system (entries 1 and 2). On the other hand, although the reaction took place readily in 1,2-dimethoxyethane (DME), tetrahydrofuran (THF), or dioxane at 70 °C under an oxygen atmosphere (1 atm), the corresponding enamides were produced as a mixture of *Z*- and *E*-enamide **3**, the former being the major isomer (entries 3−5).

On the other hand, selective formation of *Z*-enamide (*Z*/*E* >30:1) was observed in a relatively less polar solvent such as toluene, 1,2-dichloroethane, and chlorobenzene, although the conversion rate was slightly lower (entries 6−8). Among those media, the use of chlorobenzene resulted in the highest yield of *Z*-**3**. While the reaction was sluggish in the absence of Cu cocatalyst (entry 9), CuCl was superior to other copper salts examined, such as $Cu(OAc)_2$, $Cu(OTf)_2$, and CuI (<10% conversion). Interestingly, copper(II) chloride, the more typically used cocatalyst in Wacker-type reactions, displayed much lower efficiency compared to CuCl (entry 10). When benzoquinone (1.0 equiv) was used as a reoxidant instead of CuCl cocatalyst, the rate was only slightly lower, albeit with high stereoselectivity (entry 11). The oxygen atmosphere was essential for achieving high efficiency, as demonstrated in entry 12. Palladium catalysts other than $PdCl_2(PhCN)_2$ displayed lower activity in general, although the *Z*-selectivity was not changed in chlorobenzene under otherwise the same conditions. For example, conversion with $Pd(OAc)_2$ was 11%; $Pd(PPh_3)_4$, 36%; $(cod)PdCl_2$, 38%; $Pd(dba)_2$, 6%; and [1,1′-$(Ph_2P)_2$ferrocene]Cl_2Pd, <5%. Palladium complexes bearing *N*-heterocyclic carbene (NHC) ligands, such as IPrPd(allyl)Cl, $[IPrPdCl_2]_2$, and $IPrPd(O_2CCF_3)_2(OH_2)$ [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene], which have received much attention due to their air and moisture stability and increased catalytic activity, turned out to be ineffective in our case.[31]

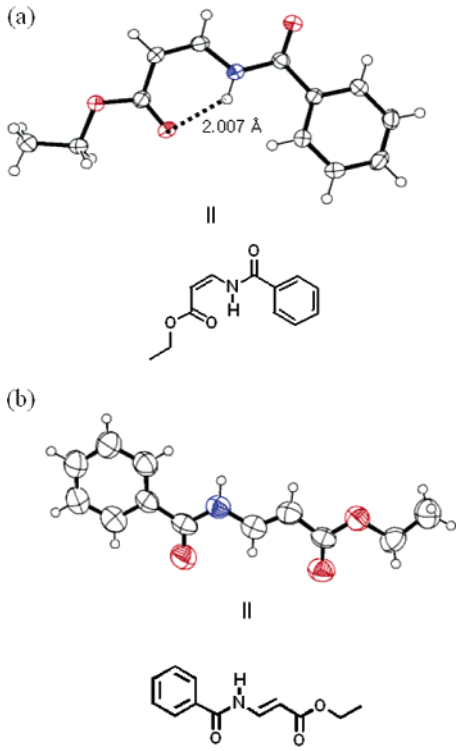


Figure 1. ORTEP drawings of (*Z*)-**3** and (*E*)-**3**.

The chemical shift of the amido hydrogen of the isolated *Z*-**3** was at 11.5 ppm ($CDCl_3$), while that of *E*-**3** appears at 8.9 ppm, strongly suggesting that an intramolecular hydrogen bond exists in the *Z*-isomer.[32] In fact, this was confirmed from crystal structure analysis of each isomer (Figure 1). The distance of the hydrogen bond (N−H···O) in *Z*-**3** was determined to be 2.007 Å from the solid structure, which is in the range of reported intramolecular H-bonds,[33] and the angle of the hydrogen-bonded N−H···O was determined to be 135.1°.

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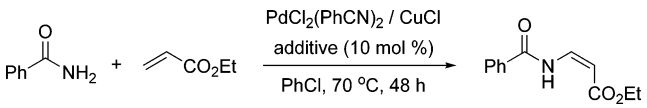
(33) (a) Kang, Y. K. *J. Phys. Chem. B* **2000**, *104*, 8321−8326. (b) Eckert, J.; Barthes, M.; Klooster, W. T.; Albinati, A.; Aznar, R.; Koetzle, T. F. *J. Phys. Chem. B* **2001**, *105*, 19−24 and refs 32a,c.

Table 2. Effects of Additives on the Oxidative Amidation[a]



entry	additive	yield (%)[b]
1		47
2	LiBr	<5
3	$(n\text{-Bu})_4N^+Cl^-$	<5
4	pyridine	<5
5	$NaHCO_3$	16
6	IPr[c]	31
7	triethylamine	<5
8	PPh_3	<5
9	$P(O)Ph_3$	68
10	$P(O)(n\text{-Oct})_3$	74[d]
11	$[(EtO)_2P(O)]_2CH_2$	72
12	HMPA	64[d]

[a] Reaction conditions: a mixture of benzamide (1 equiv), ethyl acrylate (3.0 equiv), CuCl (10 mol %), and $PdCl_2(PhCN)_2$ (5.0 mol %) in chlorobenzene (0.2 M) was stirred at 70 °C for 48 h under 1 atm of O_2. [b] In all cases, the ratio of *Z*/*E*-**3** was >30:1 and the isolated yield is that of *Z*-**3**. [c] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [d] A cyclized enamide was also obtained in ca. 10% yield, along with the desired *Z*-enamide (ref 35).

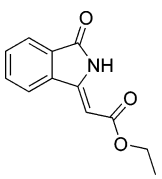
Although excellent stereoselectivity was observed for the formation of *Z*-**3** in relatively nonpolar solvents, reaction rates were retarded when compared to those in DME, THF, or dioxane, as shown in Table 1. This was mainly attributed to the formation of Pd(0) black from the palladium complex during the course of the catalytic cycles. In order to suppress such precipitation, various additives were subsequently investigated (Table 2).[34] It was observed that certain types of salts or bases significantly inhibited the reaction of benzamide with ethyl acrylate (entries 2−5). The addition of free carbene and tertiary amine, which are known to stabilize the catalyst, did not improve the yield (entries 6 and 7). In contrast, we found that, whereas the addition of phosphines or phosphonites resulted in complete inhibition, their oxides displayed notable promoting effects to accelerate the reaction rates and increase the product yields (entries 8−12). In fact, formation of palladium black was not observed in the presence of the beneficial additives. Among those examined, tetraethyl methylenediphosphonate (TEMDP) was chosen for the subsequent studies because it also inhibits formation of a side product (cyclized enamide) that is presumably formed by an intramolecular activation of the ortho proton of benzamide followed by a cyclization pathway.[35] Hexamethylphosphoramide (HMPA) displayed slightly inferior additive effects relative to phosphine oxides or TEMDP. It should be mentioned that the presence of additives did not change the stereoselectivity in the oxidative amidation; *Z*-enamides were still produced exclusively. The use of less than 3 equiv of olefins to amides resulted in decreased product yields. For example, when 2 or 1 equiv of ethyl acrylate was used under otherwise the same conditions, the product yield was 59% or 36%, respectively, compared to 72% with 3 equiv (entry 11).

Under the optimized conditions, the oxidative amidation was next investigated using a range of primary amides and conjugated olefins (Table 3). It turned out that primary amides of aryl, alkenyl, and alkyl adducts all reacted readily with olefins conjugated with any of the functional groups examined which are capable of hydrogen bonding with amido NH protons. More importantly, the enamide products were generated exclusively in *Z*-form in all cases investigated; no traces of *E*-isomers were observed. When benzamide was allowed to react with ethyl acrylate or *N*,*N*-dimethylacrylamide using $PdCl_2(PhCN)_2$ (5 mol %), CuCl (10 mol %), and TEMDP (10 mol %) in chlorobenzene at 70 °C under oxygen (48 h), the corresponding *Z*-enamides were obtained in good yields (entries 1 and 2). Since substituted vinylphosphonates have been frequently utilized as important synthetic intermediates,[36] we were interested in the oxidative amidation of those compounds. When diethyl vinylphosphonate was employed to react with benzamide, we were pleased to observe that the corresponding amidovinyl phosphonate was produced in a pure *Z*-form with a synthetically acceptable yield (entry 3). The amido proton of the produced *N*-[2-diethylphosphoryl-(*Z*)-ethenyl]benzamide appeared at 11.4 ppm ($CDCl_3$) in the ^1H NMR spectrum, implying again that a strong intramolecular H-bond exists in the product and that this is mainly responsible for the stereochemical outcome in this reaction.[37] As expected, the chemical shift of N−H in the *E*-isomeric vinylphosphonate (obtained from photoisomerization of *Z*-enamide, vide infra) was upfield (10.1 ppm) relative to that of *Z*-enamide. When methyl vinyl ketone was used, the reaction afforded the corresponding *Z*-enamide in a moderate yield but with excellent stereoselectivity, again under the same conditions (entry 4). In contrast to terminal olefins that afforded moderate to good yields of enamides, reactions with internal olefins were sluggish, resulting in lower product yields. For example, when ethyl *trans*-crotonate was applied, the *Z*-enamide was obtained in 14% yield, presumably due to the steric hindrance (entry 5).[38] It was observed that generally labile groups in Pd catalysis were tolerant under the present oxidative amidation conditions, as demonstrated by the reactions with 4-bromobenzamide (entries 6 and 7).

A range of vinylic amides were also readily reacted with conjugated olefins to afford conjugated enamides in good yields with excellent stereoselectivity for the formation of *Z*-isomers. For example, oxidative amidation of ethyl acrylate and acrylamide took place smoothly when cinnamamide was employed, to afford the corresponding *Z*-enamides in high yields (entries 8 and 9). Likewise, α-substituted vinylic amides such as methacrylamide underwent oxidative coupling with various conjugated olefins efficiently and selectively (entries 10−12). It turned out that the presence of α-substituents in the corre-

(34) Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570−1577.

(35) The side product was determined to be ethyl 3-oxo-Δ1α-isoindolineacetate.

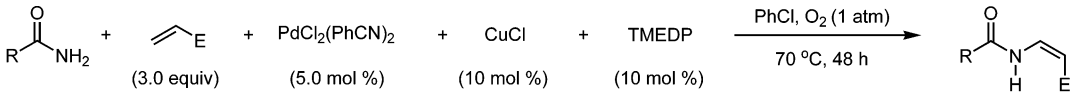


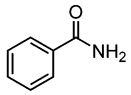
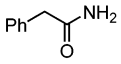
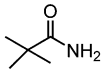
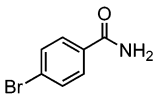
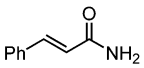
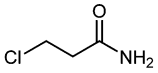
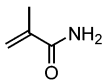
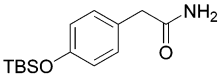
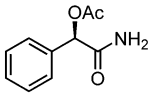
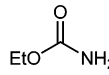
(36) For a review on the utility of vinylphosphonates, see: (a) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239−2258. (b) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177−6216. (c) Maffei, M. *Curr. Org. Synth.* **2004**, *1*, 355−375.

(37) The chemical shift of the N−H proton is not dependent upon the concentration of isolated *Z*-enamide sample. Therefore, the possibility of a contribution from an intermolecular H-bond seems to be quite low.

(38) When ethyl *cis*-crotonate and ethyl *trans*-cinnamate were applied, the corresponding enamides were not produced, which suggests that the vinyl substituents at the β position with respect to the carbonyl group of conjugated olefins might significantly inhibit the progress of the reaction.

Table 3. Oxidative Catalytic Amidation of Conjugated Olefins with Primary Amides[a]



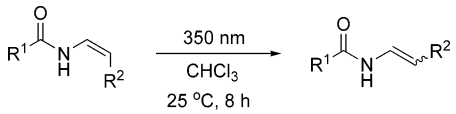
entry	amide	olefin	yield(%)[b]	entry	amide	olefin	yield(%)[b]
1		CO_2Et	70	15		$CONMe_2$	80[c]
2		$CONMe_2$	71	16		$P(O)(OEt)_2$	91[c]
3		$P(O)(OEt)_2$	59	17		$CONMe_2$	59
4		$COMe$	59				
5		CO_2Et	14	18		CO_2Et	85[c]
6		CO_2Et	54	19		$CONMe_2$	69
7		$CONMe_2$	76	20		$P(O)(OEt)_2$	77
8		CO_2Et	76	21		CO_2Et	75[c]
9		$CONMe_2$	83	22		$CONMe_2$	66[c]
10		CO_2Et	78	23		CO_2Et	81[c]
11		$CONMe_2$	82	24		$CONMe_2$	71[c]
12		$P(O)(OEt)_2$	73	25		CO_2Et	53[c]
13		CO_2Et	63	26		CO_2Et	48[d]
14		CO_2Et	82[c]				

[a] In all cases, selectivity of *Z*/*E*-isomer was >30:1, except for entry 26. [b] Isolated yields after silica gel chromatography. [c] 10 mol % of $PdCl_2(PhCN)_2$ and 20 mol % of both CuCl and TEMDP were used. [d] *Z*/*E*-isomeric ratio was 2.1:1, and the isolated yield is that of *Z*-enamide.

sponding *Z*-enamides did not interfere with the intramolecular hydrogen bond, as judged by the chemical shifts of amido protons in these cases (ca. 11 ppm in $CDCl_3$).

Aliphatic primary amides turned out to be another feasible type of substrate, producing *Z*-enamides selectively by reaction with conjugated olefins. However, in these cases, while stereoselectivity was still high for the formation of *Z*-enamides, the reactivity was generally lower than that of aromatic or vinylic amides, and larger amounts of catalysts were required to obtain satisfactory product yields. For example, while 63% yield of a *Z*-enamide was obtained from reaction of acetamide with ethyl acrylate with the use of 5 mol % of $PdCl_2(PhCN)_2$, the yield was increased to 82% by using 10 mol % of the same Pd species (compare entries 13 and 14). Under the same conditions,

Table 4. Photoisomerization of Several *Z*-Enamides



entry	R^1	R^2	*E*/*Z* (%)[a]
1	Ph	$CO_2CH_2CH_3$	4.9:1 (74)
2	Ph	$COCH_3$	5.4:1 (80)
3	Ph	$CON(CH_3)_2$	1.5:1 (56)
4	Ph	$P(O)(OCH_2CH_3)_2$	0.42:1 (31)
5	*t*-Bu	$CO_2CH_2CH_3$	0.25:1 (14)

[a] Ratio determined by ^{1}H NMR of the crude mixture, and the isolated yield is that of *E*-isomer.

acetamide was also readily reacted with other conjugated olefins to provide the corresponding *Z*-enamides in high yields (entries 15 and 16). Bulkier aliphatic amides such as phenylacetamide and trimethylacetamide underwent oxidative amidation without difficulty to afford the corresponding *Z*-enamides in good yields (entries 17−20). The amido proton peaks of *Z*-enamides obtained from the aliphatic amides appear at 10.2−11.8 ppm, depending on the substituents, while those of the *E*-isomers are found upfield (ca. 8 ppm). This indicates again that an intramolecular hydrogen bond exists in *Z*-enamides formed from aliphatic amides. The tolerance of functional groups toward the reaction conditions turned out to be respectable. Indeed, reactions of aliphatic amides substituted with halide, silyloxy, or acetoxy groups took place without problems, as demonstrated in entries 21−25.

It was observed that, when carbamates were employed as substrate, both efficiency and selectivity were significantly decreased. For example, urethane reacted with ethyl acrylate to afford a mixture of enamides (*Z*/*E*, 2.1:1) with a moderate chemical yield (entry 26). Presumably, this can be ascribed to the lower acidity of the carbamate N−H proton compared to amides and, therefore, lower stabilization of a putative σ-alkylamidopalladium adduct, leading to *Z*-isomers (vide infra).[23] On the other hand, it turned out that unconjugated simple aliphatic olefins and styrene derivatives were not viable substrates for the oxidative amidation reaction under the presently employed conditions.

It should be mentioned that a cis ↔ trans isomerization of the produced enamides does not occur under the reaction conditions. On the other hand, it is known that stereoisomers of *Z*- and *E*-enamides are interconverted by photoirradiation.[39] This led us to investigate photoisomerization of the obtained *Z*-enamides under various conditions by changing UV wavelengths and solvents. When a pure *Z*-**3** enamide was irradiated, the highest ratio of isomerization (*E*/*Z* = 4.9:1) was observed at 350 nm, and the *E*-**3** isomer could be isolated in 74% yield, along with recovered *Z*-**3** (23%), after 8 h at room temperature in chloroform (Table 4, entry 1). This result indicates that the intramolecular H-bond present in *Z*-enamides does not inhibit isomerization of the electronically excited enamides. Longer irradiation (more than 8 h) did not change the isomerization ratio, implying that a photoequilibrium was established under these conditions.[40]

Interestingly, among various solvents examined, the use of DMF or methanol, which is known to disrupt intramolecular hydrogen bonds,[41] gave a lower isomerization ratio (*E*/*Z* = 1.3−1.5:1) compared to that obtained in chloroform. The efficiency of the photoisomerization was observed to depend significantly also on the type of substituents on the enamides employed. Whereas higher ratios of photoisomerization were observed with ester or ketonyl moieties (entries 1 and 2), the *E*/*Z* ratio was sharply decreased with enamides having amido or phosphoryl groups at R^2 (entries 3 and 4). Interestingly, it was seen that a *Z*-enamide bearing an aliphatic amide was much less efficiently isomerized into the *E*-enamides, as illustrated in entry 5. Further spectroscopic and dynamic studies on the electronically excited states of enamides would be quite desirable for the quantitative explanation of our results shown in Table 4.

In Scheme 1, a plausible catalytic cycle for the present oxidative amidation is outlined using acetamide (**4**) and ethyl acrylate (**2**) as representative substrates, although several details remain to be elucidated.[42] The reaction is believed to be initiated by the displacement of the benzonitrile ligand of the palladium complex precursor, $[PdCl_2(PhCN)_2]$, by the double bond of conjugated alkene **2**, forming a palladium−olefin complex, either **A** or **B**. The palladium−olefin complex is then susceptible to intermolecular nucleophilic attack by amide **4**, which is presumably coordinated to the palladium complex prior to the nucleophilic attack,[43] leading to amidopalladation adducts **C** and/or **D** upon loss of HCl.[44]

Considering that *Z*/*E*-isomerization of enamides does not occur under the reaction conditions, it is assumed that the stereochemical outcome of the products is determined mainly after the nucleophilic attack of amide on the palladium−olefin complex.[45] It was initially considered that two intermediates, **C** and **D**, are generated without any preference for one over the other and that they actually interconvert by σ-bond rotation. However, the additional stability provided by intramolecular H-bonding in intermediate **C** is expected to drive the equilibrium between **C** and **D** toward the H-bonded intermediate **C**. In turn, the intermediate **C** is likely to undergo β-hydride elimination (via transition state **E**) more readily than the corresponding

(39) (a) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421−452. (b) Lewis, F. D.; Howard, D. K.; Oxman, J. D.; Upthagrove, A. L.; Quillen, S. L. *J. Am. Chem. Soc.* **1986**, *108*, 5964−5968. (c) Robinson, A. J.; Stanislawski, P.; Mulholland, D.; He, L.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4148−4152. (d) Kuramochi, K.; Osada, Y.; Kitahara, T. *Tetrahedron* **2003**, *59*, 9447−9454. (e) Nishio, T.; Tabata, M.; Koyama, H.; Sakamoto, M. *Helv. Chim. Acta* **2005**, *88*, 78−86.

(40) Photoirradiation of *Z*-**3** in chloroform at 300 nm gave *Z*/*E* = 1:1 within 10 min. However, after reaching *Z*/*E* = ca. 3 in 1 h, both compounds decomposed under longer irradiation. Photoirradiation of *Z*-**3** in chloroform at 250 nm resulted in decomposition of the starting material within 10 min. The time course of photoirradiation at 350 nm was monitored every 1 h.

(41) (a) Lewis, F. D.; Stern, C. L.; Yoon, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 3131−3133. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407−414 and ref 22.

(42) For recent reviews on Heck-type reactions, see: (a) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (d) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2964.

(43) Hartley, F. R. *Chem. Rev.* **1969**, *69*, 799−844.

(44) It can be also considered that the amidopalladation proceeds through zwitterionic intermediates which are deprotonated by chloride anion to afford anionic palladium species in analogy to Stahl's aerobic oxidative amination reactions, as demonstrated in ref 27.

(45) (a) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415−2434. (b) Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011−2034. (c) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188−7189. (d) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766−767. (e) Lloyd-Jones, G. C.; Slatford, P. A. *J. Am. Chem. Soc.* **2004**, *126*, 2690−2691. (f) Muller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724−9734. (g) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468−16476 and ref 42b.

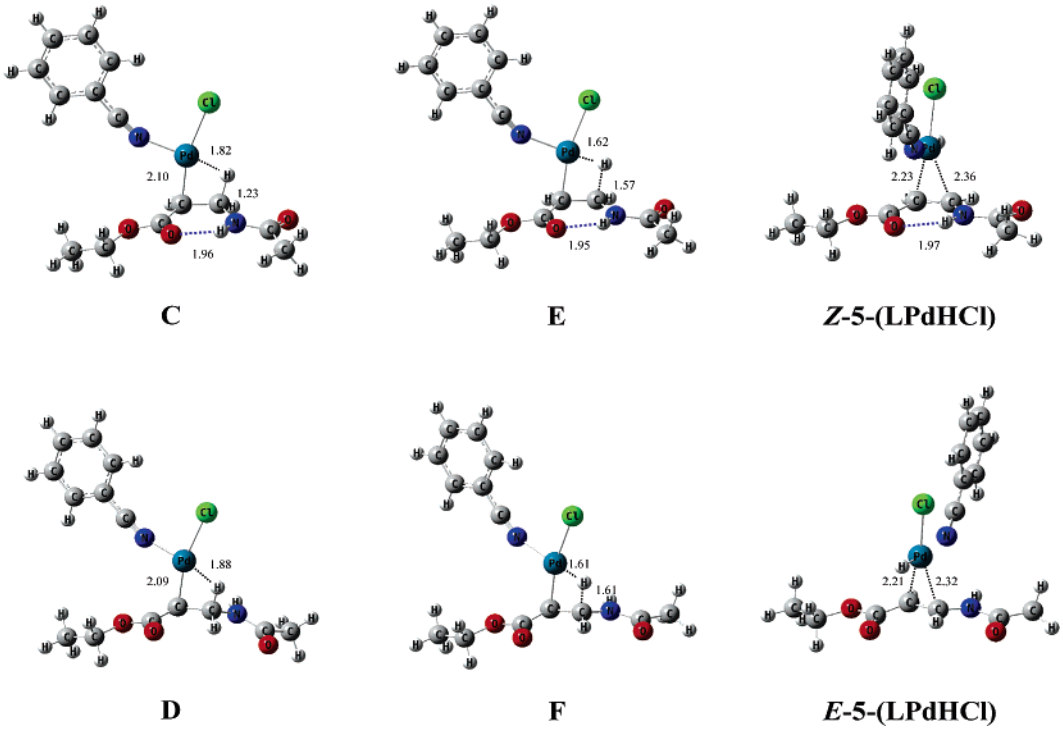
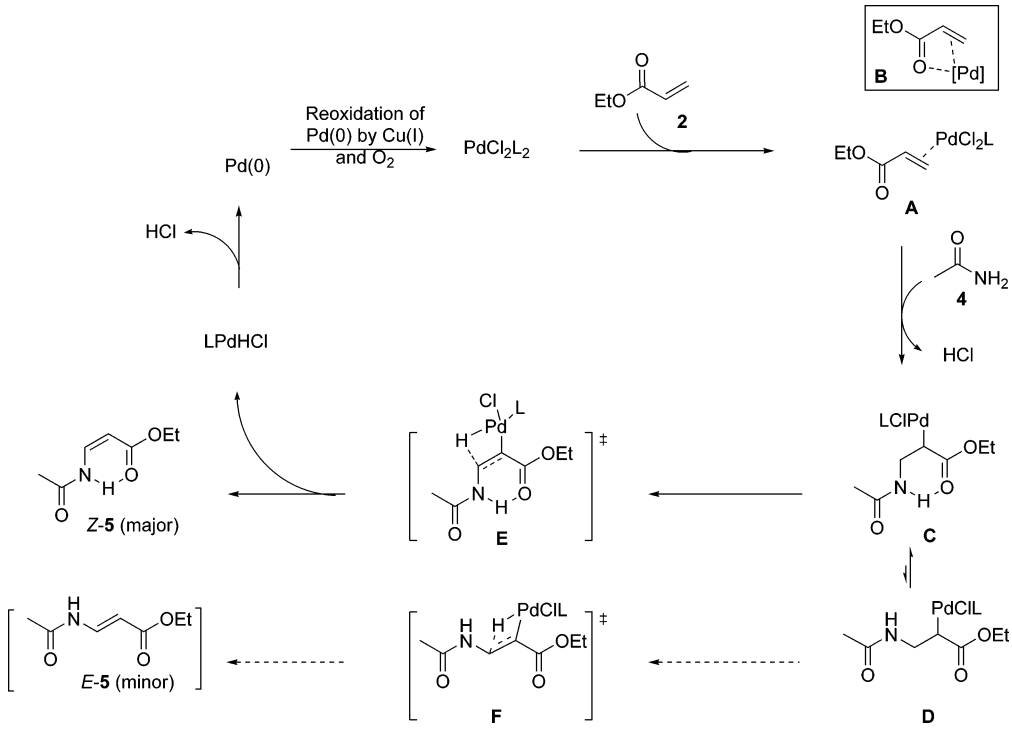


Figure 2. Optimized geometry of σ-alkylpalladium(II) intermediates and transition states for β-hydride elimination (L = PhCN).

Scheme 1



σ-alkylpalladium(II) species **D** (via transition state **F**), resulting in the predominant formation of *Z*-enamides. The LPdHCl species, which is generated from β-hydride elimination of the σ-alkylpalladium(II) intermediates in addition to enamide products, subsequently eliminates HCl to afford Pd(0), which, after oxidation by the action of copper cocatalyst and molecular oxygen in analogy to the Wacker process,[30] re-enters into the next catalytic cycle.

To rationalize the stereochemical outcome of enamide formation, optimization of stereoisomeric *Z*/*E*-enamides, plausible key intermediates **C** and **D**, and transition states of β-hydride elimination **E** and **F** (Figure 2) was carried out using the correlated ab initio and density functional theory (DFT) method B3LYP/LANL2DZ.[46] As expected, the calculation showed that isolated *Z*-**5** is more stable than its *E*-**5** isomer by 5.46 kcal/mol,[47] and coordinated species *Z*-**5**-LPdHCl is more stable than its isomer *E*-**5**-LPdHCl by 6.18 kcal/mol, probably due to the

(46) Frisch, M. J.; et al. *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2003.
(47) B3LYP/6-31G(d) is used for calculation of the energy level of final products only.

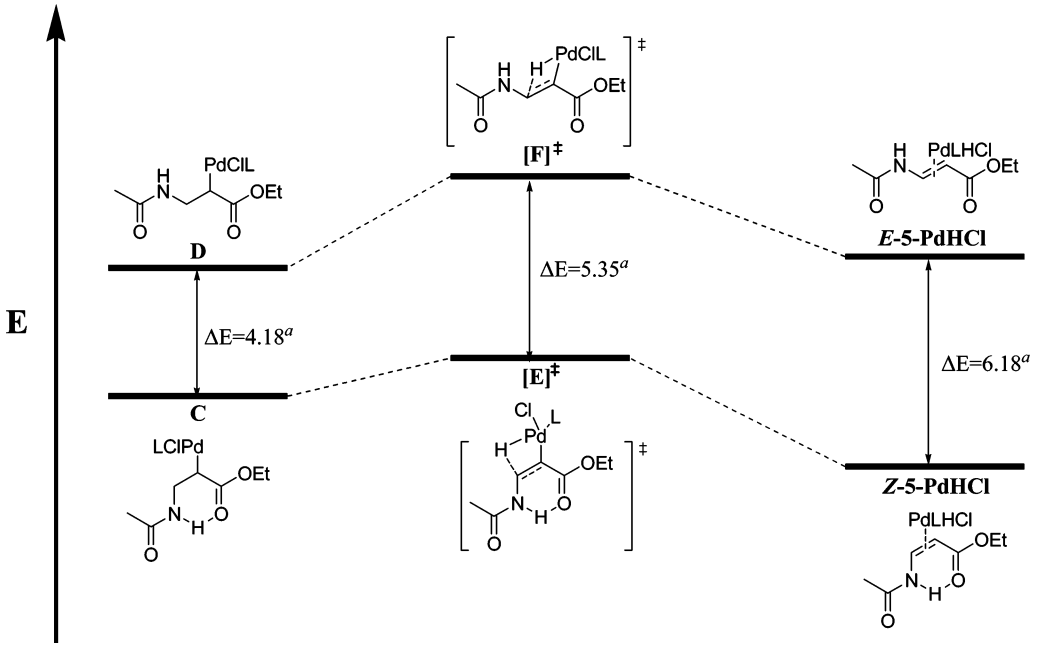
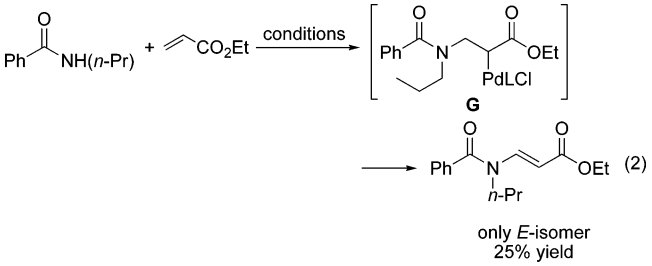


Figure 3. Relative energy diagram of geometry-optimized lowest-energy conformers of two σ-alkylpalladium(II) intermediates **C** and **D** and transition states of β-hydride elimination **E** and **F** shown in Scheme 1 ([a]energy unit is kcal/mol).

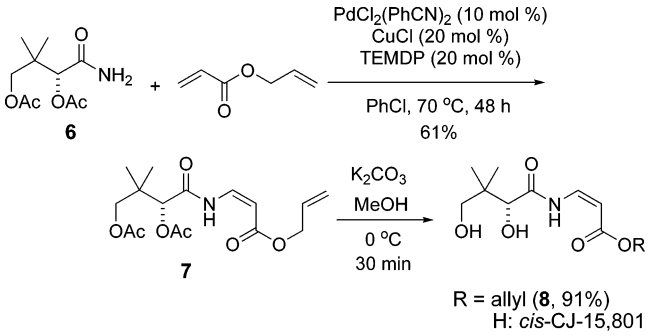
intramolecular hydrogen bonding present only in the *Z*-isomer. In addition, the energy difference between optimized amidopalladation adducts **C** and **D** (Figure 3) was calculated to be 4.18 kcal/mol, sufficiently high to explain the favorable formation of intermediate **C**. Furthermore, the energy difference between transition states **E** and **F** for β-hydride elimination leading to *Z*- and *E*-enamide, respectively, turned out to be 5.35 kcal/mol,[48] which is again sufficiently large to ensure almost exclusive generation of the *Z*-enamide. This led us to assume that β-hydride elimination from the σ-alkylpalladium(II) intermediates, leading to enamide products, is a stereochemistry-determining step in the overall oxidative amidation process.[49]

When a secondary amide was employed under otherwise the identical conditions, the oxidative amidation of ethyl acrylate was very sluggish and produced the *E*-enamide exclusively, but in only poor yield (eq 2). This result may be explained by



considering that a putative H-bond does not exist in the corresponding σ-alkylpalladium(II) intermediate (**G**); thus, only the thermodynamically more stable *E*-enamide is formed in this case. We believe that this result further supports our proposal that an intramolecular H-bond in the plausible σ-alkylamidopalladium intermediates not only accelerates the reaction rates but also controls the stereoselectivity of the produced enamides, most probably through the β-hydride elimination step.[50]

Scheme 2



A novel *N*-acyl vinylogous carbamic acid, CJ-15,801, was recently reported as an inhibitor of multiple-drug-resistant (MDR) *Staphylococcus aureus* strains.[51] We envisioned that our method could be effectively utilized for the direct synthesis of *cis*-CJ-15,801 by employing a functionalized amide and acrylic ester (Scheme 2).[52] When a suitable amide (**6**), derived from *R*-(+)-pantolactone,[53] was allowed to react with allyl acrylate under the oxidative amidation conditions developed in this study, the reaction took place readily to afford the corresponding *Z*-enamide (*Z*-**7**) in good yield and with excellent stereoselectivity (*Z*/*E* >30:1). Two acetate groups were then efficiently deprotected under the standard conditions to afford *Z*-**8** in excellent yield, thus achieving a truly efficient and direct formal synthesis of *cis*-CJ-15,801.[54]

(48) E_a for **F** is 1.46 kcal/mol and E_a for **E** is 0.29 kcal/mol.
(49) For examples of β-hydride elimination as a rate-determining step by the similar approach, see ref 45g.
(50) For an intuitive review on the issue of reactivity and selectivity in catalysis, see: Zaera, F. *Catal. Lett.* **2003**, *91*, 1−10.
(51) Sugie, Y.; Dekker, K. A.; Hirai, H.; Ichiba, T.; Ishiguro, M.; Shiomi, Y.; Sugiura, A.; Brennan, L.; Duignan, J.; Huang, L. H.; Sutcliffe, J.; Kojima, Y. *J. Antibiot.* **2001**, *54*, 1060−1065.
(52) For the Cu-mediated *N*-vinylation of amides with (*E*)-allyl-β-iodoacrylate for the synthesis of CJ-15,801 and its analogues, see ref 23.
(53) For the preparation of amide, see: Harris, S. A.; Boyack, G. A.; Folkers, K. *J. Am. Chem. Soc.* **1941**, *63*, 2662−2667.
(54) For the deallylation procedure from the same precursor to give free *cis*-CJ-15,801, see ref 21.

Conclusions

We have shown that *Z*-enamides can be efficiently prepared in high yields and with excellent stereoselectivity by the direct reaction of primary amides with conjugated olefins under Wacker-type conditions. A wide range of amides are readily reacted with acrylic esters, acrylic amides, alkyl vinyl ketones, and vinyl phosphonate by the action of a Pd/Cu cocatalyst system under an oxygen atmosphere, leading to the corresponding enamides exclusively in the *Z*-form. The high stereoselectivity observed in this study is mainly attributed to the favorable β-hydride elimination from one plausible σ-alkylamidopalladium intermediate which bears an intramolecular hydrogen bond. In fact, the energy difference between two proposed amidopalladation intermediates was calculated to be 4.18 kcal/mol, where the intermediate having an intramolecular H-bond is more stable. Moreover, a transition state of β-hydride elimination leading to the *Z*-enamide was determined to be more stable by 5.35 kcal/mol compared to that resulting in the *E*-isomer, implying that the stereochemistry-determining-step in the present oxidative amidation reactions is closely related to the β-hydride elimination of the σ-alkylamidopalladium intermediates. Efficiency in the photoisomerization of *Z*-enamides into the corresponding *E*-isomers was observed to be dependent on the type of substituents of enamide substrates and solvents employed, and synthetically useful yields of *E*-enamides could be obtained with *Z*-enamides having more acidic amido protons. Considering its convenient reaction conditions and excellent stereoselectivity, the present oxidative amidation procedure should attract much interest as a synthetically feasible approach for the preparation of *Z*-enamides from readily available starting materials.

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Supporting Information Available: Complete ref 46, experimental procedures, characterization of products, copies of ^{1}H and ^{13}C NMR spectra of the obtained enamides, X-ray crystallographic data of *Z*-**3** and *E*-**3**, and XYZ coordinates for the calculated compounds/transition states (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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