ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

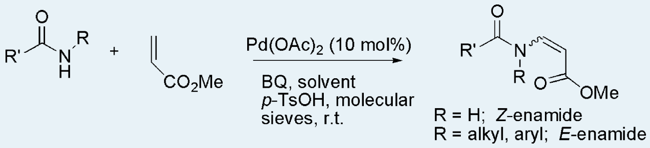
# Stereoselective Synthesis of Enamides by Palladium Catalyzed Coupling of Amides with Electron Deficient Olefins

Niranjan Panda,* Ashis K. Jena,† and M. Raghavender†

Department of Chemistry, National Institute of Technology, Rourkela-769008, Odisha, India

Supporting Information

**ABSTRACT:** A copper-free palladium-catalyzed convenient and efficient oxidative amidation protocol for synthesis of enamides by the cross-coupling of amides with acrylate has been developed. The thermodynamically disfavored *Z*-isomers are accessible by the intramolecular hydrogen bonding between the amido proton and carbonyl oxygen. The reactions were found to be acid catalyzed and *p*-TsOH gave the best result in enamide synthesis. The reactions were conducted at room temperature in presence of ambient air. This protocol has wide substrate scope allowing alkyl, aryl, substituted arylamides, urea, and its derivatives to react with methyl acrylate. The reactions are found to be tolerant to the steric demand of secondary amides and give the tertiary *E*-enamides in moderated to good yield.



**KEYWORDS:** *enamides, tertiary enamides, palladium, oxidative amidation, methyl acrylate*

## ■ INTRODUCTION

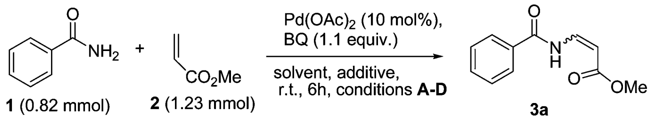
Enamide being a versatile synthetic intermediate, has been widely utilized in the formation of chiral amines, amino acids, and numerous heterocycles.[1−4] Additionally, the enamide motif also appears in a number of biologically active natural products[5] such as salicylihalamides,[6] lansiumamide A,[7−10] TMC-95A-D,[11] crocacin,[12] alatamide,[13−15] and a range of marine metabolites.[16] Considering the extensive pervasiveness of enamides, several methods have emerged for their synthesis. The conventional methods include condensation of aldehydes and ketones with amides[17,18] or dehydration of hemiaminals,[10,19] acylation of imines,[20−22] Curtius rearrangement of $\alpha$, $\beta$-unsaturated acyl azides,[8,23,24] and elimination of $\beta$-hydroxy-$\alpha$-silylamides (Peterson reaction).[9,25,26] Besides, Pd- and/or Cu-catalyzed cross-coupling of vinyl derivatives (viz., halides,[27−32] triflates,[33] tosylates,[34] borates,[35] ethers[36]) with amides have been found to be another attractive protocol to access a wide range enamides. However, these methods often require rigorous conditions, such as exclusion of moisture and air, elevated temperature, and utilization of excess strong base.[37] The proper functionalization of the coupling partner (i.e., vinyl substrate) often suffers from low yield or intricacy in preparation.[38] Stereocontrol of the double bond presents another potential problem, particularly in the synthesis of thermodynamically disfavored *Z*-enamides.[39] Thus, it is highly desirable to develop general and practical methods for the stereoselective preparation of enamides, using simple and readily available vinyl substrates. Evidently, direct oxidative amidation of the olefins have been exploited as a possible alternative to overcome these limitations, and some elegant methods have been disclosed. For instance, Hirai and Sawai reported the synthesis of enamide by the coupling reaction of cyclic amides with ethylene-palladium-chloride.[40] Murahashi and co-workers[41] revealed the $PdCl_2(MeCN)_2/CuCl$-catalyzed amidation of electron deficient olefins. Stahl and co-workers[42−44] described the Pd-catalyzed aerobic oxidative amidation of unactivated alkenes. Chang et al.[45] also contributed a Pd/Cu-catalyzed protocol for the selective synthesis of *Z*-enamide from the acyclic amides. More recently, Liu and Hii[46] reported a chloride-free, Pd/Cu cocatalyzed system for the cross-coupling of olefins with electron rich amides. Although these achievements are promising, limited substrate scope, poor stereoselectivity, and requirement of ambient reaction conditions often demand new catalytic systems that can further improve the reaction efficiency and scope, thus making this approach more attractive. Herein, we reveal a highly efficient, copper-free, Pd-catalyzed protocol for direct amidation of electron deficient olefins. This reaction proceeds at room temperature with wide substrate scope and results in some novel enamides with high *Z*-selectivity. Our catalytic system is also found to be suitable for the synthesis of trisubstituted enamides in appreciable yield from the sterically hindered secondary amides even at room temperature, which is considered as a significant challenge in recent years.[47]

## ■ RESULTS AND DISCUSSIONS

We initiated our study by conducting the $Pd(OAc)_2$-catalyzed oxidative amidation of methyl acrylate with benzamide (**1**) under various reaction conditions (Table 1). We observed that solvent polarity has a significant effect on the efficiency and selectivity of the process. For instance, when reaction was carried out in polar solvents like dimethylsulfoxide (DMSO), dimethylformamide (DMF), tetrahydrofuran (THF), and so forth the starting material was not completely consumed even

**Received:** December 2, 2011
**Revised:** February 16, 2012
**Published:** March 8, 2012

**Table 1. Reaction Condition Optimization in Oxidative Amidation**[a]



| entry | solvent | additives | condition | % yield (*Z*:*E*) |
|---|---|---|---|---|
| 1 | toluene | | A | 00 |
| 2 | toluene | AcOH (1 mL) | A | 38 (*Z* only) |
| 3 | toluene | *p*-TsOH (0.5 equiv) | A | 66 (*Z* only) |
| 4 | toluene | *p*-TsOH (0.5 equiv) | B | 60 (*Z* only) |
| **5** | **toluene** | ***p*-TsOH (0.5 equiv)** | **C** | **76** (*Z* only) |
| 6 | toluene | *p*-TsOH (0.5 equiv) | D | 55 (2:1) |
| 7 | 1,4-dioxane | *p*-TsOH (0.5 equiv) | C | 62 (25:1) |
| 8 | DCE | *p*-TsOH (0.5 equiv) | A | 45 (3.3: 1) |
| 10 | THF | *p*-TsOH (0.5 equiv) | A | 40 (1:9) |
| 11 | DMF | *p*-TsOH (0.5 equiv) | A | 32 (1:10) |
| 12 | DMSO | *p*-TsOH (0.5 equiv) | A | 35 (1:13) |
| 13 | toluene/$H_2O$ (4:1) | *p*-TsOH (0.5 equiv) | A | 40 (*Z* only) |

[a] Conditions **A**: air; **B**: molecular sieves (4 A°), $N_2$ atmosphere; **C**: molecular sieves 4 A°, air; **D**: $Cu(OAc)_2$ (10 mol %), air.

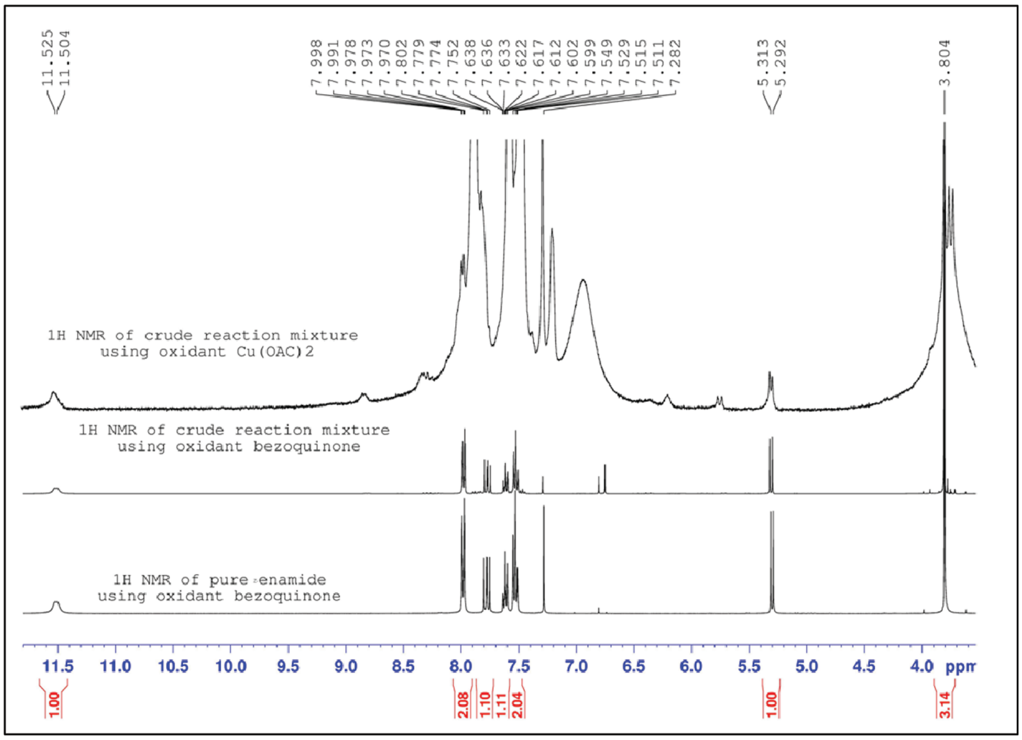
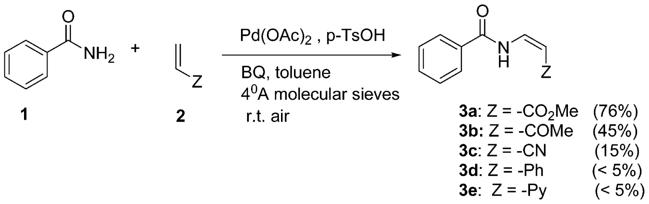


**Figure 1.** Comparison of NMR spectra using BQ and $Cu(OAc)_2$ as oxidant.

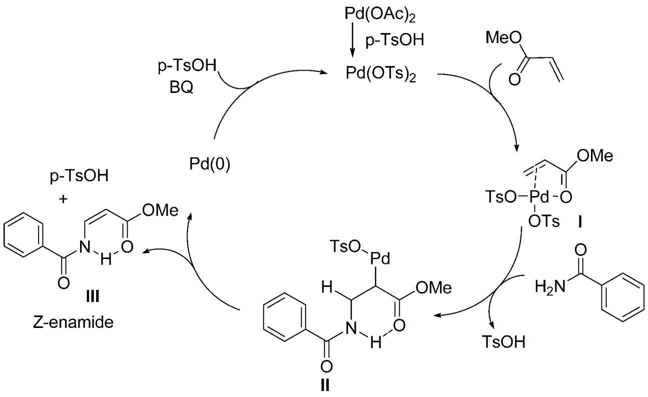
after 24 h and resulted in poor yield of the enamide (**3a**) along with the formation of polymerized products (Table 1, entries 7−12). Additionally in polar solvents, selectivity of the reaction lost with the formation more amount of *E*-isomer (see Supporting Information for comparison). In contrast, when the reaction was carried out in nonpolar solvent like toluene, the amidation reaction proceeded smoothly and gave 76% of *Z*-enamide **3a** selectively (Table 1, entry 5). Presence of acid is found to be very crucial.[48] The reaction proceeds well in presence of acetic acid; however, addition of 0.5−1.0 equiv of *p*-TsOH results in the best yield of **3a**. Without acid the reaction does not proceed even in presence of oxidant. Evidently, this is due to the in situ formation of a reactive palladium mono- or bistosylate species[49] from the $Pd(OAc)_2$ precatalyst which results in the increase of the electrophilicity of Pd(II) center for faster metalation of methyl acrylate. Instead of taking TsOH as additives, when 10 mol % of $Pd(OTs)_2$ was taken directly in the amidation reaction, the yield of **3a** then reduced to 24%. Thus, excess of Brønsted acid is found to be beneficial to improve the efficiency of catalytic process. When the amidation reaction was conducted in toluene at room temperature using $Cu(OAc)_2$ as oxidant, a mixture of *E* and *Z*-enamides was obtained (Table 1, entry 6) and in turn this is in agreement with the observations of Liu and Hii.[46] In contrast, when benzoquinone (BQ) was used as oxidant in place of $Cu(OAc)_2$ only *Z*-enamide (**3a**) was obtained (see Figure 1). Moreover, examples on Cu(II)-mediated isomerization of amides have literature precedent.[50] It is believed that BQ not only serves as an oxidant but also acts as ligand to stabilize the different palladium species that resulted in the catalytic cycle.[48,51−54] Indeed, use of BQ as ligand for Pd species has literature precedent. For example, Covell and White illustrated the formation of [(*π*-allyl) Pd(BQ)OAc] intermediate in the enantioselective allylic C−H oxidation of terminal olefins.[55] Le Bras and co-workers[56] also reported that BQ acts both as an oxidant and a ligand to stabilize Pd(0) by avoiding the formation of Pd black, thus facilitating the overall transformation. Eventually it became apparent that water was detrimental to the reaction, and by employing molecular sieves with toluene as solvent, **3a** was obtained in 76% yield after 6 h stirring at room temperature. The yield of the reaction was almost unaffected even after prolonged stirring for 24 h. It may be noted that increase in the catalyst loading from 10 to 20 to 50 mol % does not improve the product yield appreciably, though the reason is unclear presently. It may be assumed that increased catalyst loading or prolonged stirring of the reaction mixture causes competitive polymerization.[46] Use of 1 equiv of acetic anhydride instead of molecular sieves as a drying agent resulted in 60% yield of the enamide consistently, and this is in line with the observations of Loyd-Jones and Booker-Milburn[49] for C−H activation. Furthermore, increase of reaction temperature (room temperature to 60 °C) has no accelerating effect on the reaction rate; rather, the yield of the product reduced because of the possible polymerization. When the product **3a** was heated with $Pd(OAc)_2$, BQ, *p*-TsOH in presence of molecular sieves in toluene at 60 °C, complete decomposition takes place. The use of excess amount of amide or olefin does not affect the product yield significantly. Another important observation in the oxidative amidation is that the reaction proceeds successfully in presence of ambient air. In presence of $N_2$ atmosphere the reaction becomes sluggish and results in 60% yield of **3a**. To ascertain this catalytic process as a "copper-free" catalytic process,[57] chemical analysis of the $Pd(OAc)_2$ sample was performed using atomic absorption spectroscopy, and we did not detect any trace of Cu even at parts per million (ppm) level.

**Scheme 1. Cross-Coupling of Benzamide with Olefins**



With these optimized conditions in hand, we explored the scope of the reaction with a variety of substituted alkenes (Scheme 1). With the parent system **1** it was found that electron-deficient alkenes made the best coupling partners, and unactivated alkenes such as styrene and 4-vinylpyridine were inactive to give the corresponding enamide. Interestingly, under our reaction conditions the former coupling partners exclusively give the *Z*-enamides, and we did not found any trace of *E*-isomer in the crude reaction mixture from NMR study (Figure 1). Formation of *Z*-enamide is evident from the spectral data. For example, the appearance of doublets at $\delta$ 11.5 (for N−H) and 5.27 (vinylic proton) with coupling constant 8.8 Hz reveals the formation of *Z*-enamide.[45] On the basis of the earlier work by Chang and co-workers, we suggest an analogous mechanism[45] for the oxidative amidation of benzamide and methyl acrylate (Scheme 2) to explain the *Z*-selectivity of the reaction. Evidently, the palladium mono- or bistosylate generated from $Pd(OAc)_2$ undergoes oxidative addition with methyl acrylate to give palladium-olefine complex (**I**).

**Scheme 2. Catalytic Cycle for Z-Enamide Synthesis**

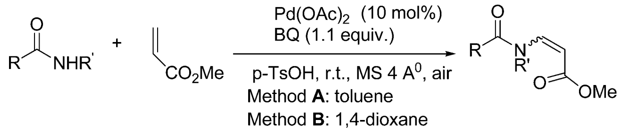


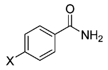
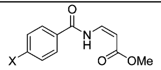
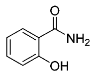
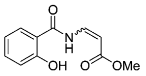
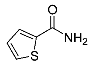
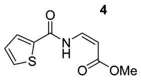
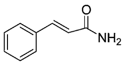
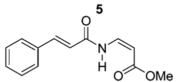
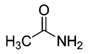
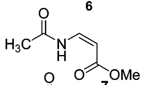
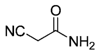
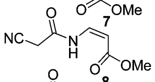
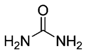
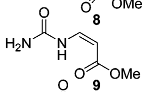
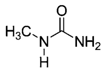
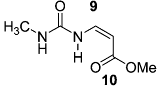
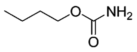
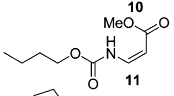
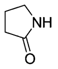
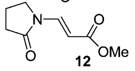
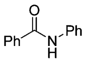
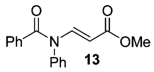
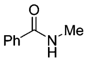
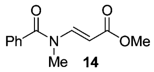
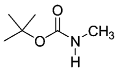
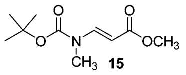
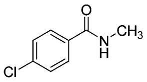
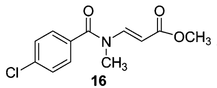
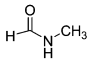
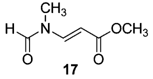
Nucleophilic attack of amide to the complex **I**, leads to the hydrogen bonded *σ*-alkylpalladium tosylate complex **II**. Subsequent *β*-hydride elimination from the hydrogen bonded complex **II**, results in the *Z*-enamide exclusively.

Next we extended the scope of the oxidative amidation reaction using a range of amides with methyl acrylate (Table 2). It turned out that primary amides of alkyl and aryl adducts cross-couple with methyl acrylate and lead to the *Z*-enamides. This catalytic protocol was found to be tolerant to aryl ring substitutions, and in most cases moderate to good yields of enamides were obtained. As such, electron withdrawing substituents (i.e., $-NO_2$, Cl) that decrease the nucleophilicity of amide still couple with methyl acrylate and lead to the *Z*-enamides in good yield without affecting the selectivity (Table 2, entries: 3−5). In contrast, when salicylamide reacts with methyl acrylate (Table 2, entry 6), it results in the mixture of *E*/*Z*- isomers (see Supporting Information for spectral evidence). This may be due to the favorable intramolecular hydrogen-bonding in salicylamide (-HO···H−N), which inhibits the extent of hydrogen bonding between N−H and C═O group of methyl acrylate (Scheme 3).

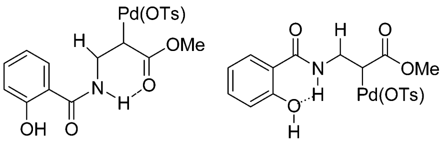
Urea and carbamates underwent cross-coupling with methyl acrylate and furnished some novel enamides in modest yield. Reactions of ureas resulted in *Z*-enamides, with functionalization of only one of the nitrogen atoms (Table 2, entries 11 and 12), even in the presence of excess methyl acrylate. When cyclic amide such as pyrrolidinone was subjected to cross-coupling with methyl acrylate, only the thermodynamically favorable *E*-enamide ($J$ = 14 Hz) was obtained (Table 2, entry 14). This again substantiates the significance of intramolecular hydrogen bonding in enamide synthesis. Finally, scope of our protocol has been extended to the sterically hindered enamides (Table 2, entries 15−19). In the earlier system reported by Liu and Hii,[46] the reaction of acyclic sterically more hindered secondary amides, such as *N*-methyl acetamide, *N*-methyl benzamide with butyl acrylate was found to be ineffective (<5%) despite their higher nucleophilicity. Benzanilide undergo ortho C−H bond activation under similar reaction conditions.[51] Moreover, formation of tertiary enamides from sterically hindered secondary amides has less literature precedent.[47] To our pleasure, the developed catalytic system was found to be

**Table 2. Enamide Synthesis**



| Entry | Substrate | Product | Method | time (h) | Yield, % |
|---|---|---|---|---|---|
| |  |  | | | |
| 1 | X= H | **1a** | **A** | 6 | 76 |
| 2 | X = 4-OMe | **3g** | **A** | 12 | 65 |
| 3 | X= 4-Cl | **3h** | **A** | 28 | 40 |
| 4 | X = 2-Cl | **3i** | **A** | 10 | 64 |
| 5 | X = 4-NO$_2$ | **3j** | **B** | 10 | 48 |
| 6 |  |  **4** | A | 12 | 57 (9:1) |
| 7 |  |  **5** | A | 10 | 63 |
| 8 |  |  **6** | B | 12 | 55 |
| 9 |  |  **7** | B | 10 | 46 |
| 10 |  |  **8** | A/B | 24 | 00 |
| 11 |  |  **9** | B | 10 | 45 |
| 12 |  |  **10** | B | 12 | 40 |
| 13 |  |  **11** | A | 12 | 64 |
| 14 |  |  **12** | A | 12 | 65 |
| 15 |  |  **13** | A | 36 | 45 |
| 16 |  |  **14** | A | 36 | 35 |
| 17 |  |  **15** | A | 10 | 56 |
| 18 |  |  **16** | A | 24 | 40 |
| 19 |  |  **17** | A | 12 | 63 |

**Scheme 3. Hypothetical σ-Alkylpalladium Tosylate Complex**


**IV** **V**

tolerant to such steric hindrance offered by the secondary amides such as benzanilides and carbamates and furnish tertiary enamides in good yield even at room temperature.

## CONCLUSION

We have demonstrated an improved catalytic protocol for the oxidative amidation of olefins in presence of ambient air. A wide range of amides and olefins were found to be reactive for the generation of enamides at room temperature. The high stereoselectivity is mainly attributed to the favorable β-hydride elimination from the hydrogen bonded σ-alkylpalladium tosylate intermediate. This protocol is found to be suitable for the cross coupling of sterically hindered secondary amides with electron deficient olefins leading to tertiary enamides in good yield. We strongly believe that the distinct simplicity of this catalytic system would render its wide usage useful in organic synthesis. Studies along these lines are ongoing in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Synthesis and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

### Corresponding Author

*E-mail: npanda@nitrkl.ac.in, Phone: +91 661 2462653.

### Author Contributions

†Contributed equally.

### Funding

The authors are thankful to the Director, NIT Rourkela and DST, India, for financial support.

### Notes

The authors declare no competing financial interest.

## REFERENCES

(1) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679−1681.
(2) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363−372.
(3) Sibi, M. P.; Asano, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9708−9709.
(4) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103−151.
(5) Yet, L. *Chem. Rev.* **2003**, *103*, 4283−4306.
(6) Erickson, K. L.; Beutler, J. A.; Cardellina, I. I., J. H.; Boyd, H. M. R. *J. Org. Chem.* **1997**, *62*, 8188−8192.
(7) Lin, J.-H. *Phytochemistry* **1989**, *28*, 621−622.
(8) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735−3738.
(9) Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955−3957.
(10) Bayer, A.; Maier, M. E. *Tetrahedron* **2004**, *60*, 6665−6677.
(11) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kurado, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990−995.
(12) Kunze, B.; Jansen, R.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881−886.
(13) Ghosh, S.; Datta, D. B.; Sen, N. *Synth. Commun.* **1987**, *17*, 299−307.
(14) Maxwell, A.; Rampersad, D. *J. Nat. Prod.* **1989**, *52*, 411−414.
(15) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Seijas, J. A.; Castedo, L. *Synth. Commun.* **1990**, *20*, 503−507.
(16) For reviews, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155−198. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7−55.
(17) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479−1482.

(18) Dupau, P.; Le Gendre, P.; Brueau, C.; Dixneuf, P. H. *Synlett* **1999**, 1832–1834.
(19) Wang, X.; Porco, J. A. Jr. *J. Org. Chem.* **2001**, *66*, 8215–8221.
(20) Boeckman, R. K. Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250–8252.
(21) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.
(22) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045–2048.
(23) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185–2195.
(24) Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397–399.
(25) Ager, D. J. *Synthesis* **1984**, 384–398.
(26) Ager, D. J. *Org. React.* **1990**, *38*, 1–223.
(27) For a review, see: Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973–986.
(28) Ogawa, T.; Kiji, T.; Hayashi, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443–1446.
(29) Shen, R.; Porco, J. A. Jr. *Org. Lett.* **2000**, *2*, 1333–1336.
(30) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669.
(31) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809–1812.
(32) Kozawa, Y.; Mori, M. *J. Org. Chem.* **2003**, *68*, 3064–3067.
(33) Wallace, D. J.; Klauber, D. J.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749–4752.
(34) Klapars, A.; Campos, K. R.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185–1188.
(35) Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2109–2112.
(36) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848.
(37) Lu, Z.; Kong, W.; Yuan, Z.; Zhao, X.; Zhu, G. *J. Org. Chem.* **2011**, *76*, 8524–8529.
(38) Arndt, M.; Salih, K. S. M.; Fromm, A.; Goossen, L. J.; Menges, F.; Niedner-Schatteburg, G. *J. Am. Chem. Soc.* **2011**, *133*, 7428–7449.
(39) Goossen., L. J.; Salih, K. S.; Blanchot, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8492–8495.
(40) Hirai, H.; Sawai, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2208–2213.
(41) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. *Tetradedron Lett.* **1992**, *33*, 6643–6646.
(42) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996–12997.
(43) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868–2869.
(44) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888–17893.
(45) Lee, J. M.; Ahn, D.-S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. *J. Am. Chem. Soc.* **2006**, *128*, 12954–12962.
(46) Liu, X.; Hii, K. K. *Eur. J. Org. Chem.* **2010**, 5181–5189.
(47) Liu, Y.; Li, D.; Park, C.-M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7333–7336.
(48) Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790–1793.
(49) Houlden, C. E.; Bailey, C. D.; Gair Ford, J.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066–10067.
(50) Cox, C.; Lectka, T. *Acc. Chem. Res.* **2000**, *33*, 849–858 , and references therein.
(51) Boele, M. D. K.; van Strijdonck, G. P. F; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P.W.N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.
(52) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097–2100.
(53) Bäckvall, J.-E. *Pure Appl. Chem.* **1992**, *64*, 429–437.
(54) Roffia, P.; Conti, F.; Gregorio, G.; Pregaglia, G. F.; Ugo, R. *J. Organomet. Chem.* **1973**, *391*, 391–394.
(55) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448–6451.
(56) Aouf, C.; Thiery, E.; Le Bras, J.; Muzart, J. *Org. Lett.* **2009**, *11*, 4096–4099.
(57) Corma, A.; Juárez, R.; Boronat, M.; Sánchez, F.; Iglesias, M.; García, H. *Chem. Commun.* **2011**, *47*, 1446–1448.