C−H Activation

DOI: 10.1002/ange.201307942

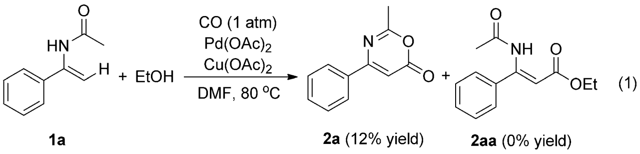
Palladium-Catalyzed Oxidative Carbonylation of the Alkenyl C−H Bonds of Enamides: Synthesis of 1,3-Oxazin-6-ones**

*Ming Chen, Zhi-Hui Ren, Yao-Yu Wang, and Zheng-Hui Guan**

Carbonylation reactions with CO have been and continue to be a very active area of research.[1] Transition-metal-catalyzed carbonylation of organic halides,[2] hydroformylation of alkenes,[3] and carbonylations for acetic acid and acetic anhydride processes[4] have been demonstrated as powerful and practical methods to synthesize various of carbonyl compounds. In recent decades, much progress has been made in transition-metal-catalyzed C−H bond activation and functionalization.[5] Ruthenium-catalyzed carbonylation of C−H bonds with CO and olefins has been developed for the synthesis of aryl alkyl ketones by Murai, Chatani, and coworkers.[6] Recently, palladium- and rhodium-catalyzed carbonylation of aromatic C−H bonds for atom-economical construction of aromatic carbonyl compounds have been developed by several groups, including ours.[7] However, transition-metal-catalyzed alkenyl C−H bond activation and carbonylation with CO for the direct synthesis of α,β-unsaturated carbonyl compounds has not yet been realized.[8]

Enamides and their derivatives are versatile building blocks in organic synthesis.[9] Asymmetric hydrogenation of enamides and 1,2-nucleophilic addition of enamides to active electrophiles have been developed for the synthesis of pharmaceutical chiral amines.[10] Recently, transition-metal-catalyzed cross-coupling of the C−H bonds of enamides with alkynes or organometallic regents for the construction of aza-heterocycles have received significant attention.[11] In connection with our interest in the C−H bond carbonylation,[7a,b] we hypothesized that palladium-catalyzed oxidative carbonylation of the C−H bond of an enamide may be achieved under a CO atmosphere. However, the execution of this carbonylation reaction faces a formidable challenge: palladium-catalyzed C−H carbonylation preferentially proceeds under acidic conditions, thus generating highly electrophilic cationic palladium(II) species[7c,d] and inhibiting the possible reduction of Pd^{II} to Pd^0 by CO,[7b–c,12] but enamides cannot be tolerated under acidic conditions.[10,11] Herein, we describe the development of a palladium-catalyzed oxidative alkenyl C−H bond carbonylation for the synthesis of 1,3-oxazin-6-ones under mild reaction conditions.

We began our study with the palladium-catalyzed carbonylation of the enamide **1a** with CO and ethanol. The carbonylation product, the 1,3-oxazin-6-one **2a**, was formed in 12% yield instead of the ethoxycarbonylation product **2aa** [Eq. (1); DMF = *N*,*N*-dimethylformamide]. Importantly, the carbonylation of the alkenyl C−H bond of enamide was observed. 1,3-Oxazin-6-ones are a class of important six-membered heterocyclic compounds. Present methods for the synthesis of 1,3-oxazin-6-ones involve the ring enlargement of isoxazol-5-ones or thermolysis of 1,3-dioxane-4,6-diones.[13] The C−H carbonylation of enamides for the synthesis of 1,3-oxazin-6-ones would be an ideal and environmentally friendly approach to this structure.



Therefore, the carbonylation reaction conditions were optimized (Table 1). KI which has been shown to improve the efficiency of palladium-catalyzed carbonylations was used in the reaction as an additive.[7a,14] The yield of **2a** was improved to 25% (Table 1, entry 2). By screening various solvents, such as CH_3CN, toluene, and THF, we found that DMF was still is the most effective solvent (Table 1, entries 3–5). Increasing the loading of KI resulted in a 35% yield of **2a**. However, further increasing the loading of KI resulted in no improvement (Table 1, entry 6). Next, acetic anhydride, which may inhibit the possible reduction of the active palladium(II) catalyst intermediate to inactive palladium(0) by CO, was added to the reaction,[7b–c,12] and the yield **2a** was improved to 45% (Table 1, entry 7). To further improve the reaction outcome, various bases were screened. Among of various inorganic bases and organic bases, DABCO (1,4-diazabicyclo-[2.2.2]octane) was found to be the most effective for this carbonylation reaction, thus giving **2a** in 84% yield (Table 1, entries 8–12).

With the optimized reaction conditions established, the scope of the reaction was investigated (Table 2). This new carbonylation reaction displayed high functional-group tolerance and proved to be a quite general methodology. Aryl enamides with methyl, phenyl, methoxyl, [1,3]dioxole, amino, fluoro, and sensitive functional groups such as chloro and bromo groups on the aromatic rings all gave the correspond-

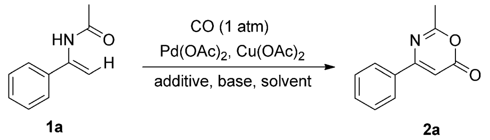
---

[*] M. Chen, Z.-H. Ren, Prof. Y.-Y. Wang, Prof. Dr. Z.-H. Guan
Key Laboratory of Synthetic and Natural Functional Molecule
Chemistry of Ministry of Education, Department of Chemistry &
Materials Science, Northwest University
Xi'an, 710069 (P. R. China)
E-mail: guanzhh@nwu.edu.cn
Homepage: http://chem.nwu.edu.cn/teacher.php?id=189

[**] This work was supported by generous grants from the National Natural Science Foundation of China (NSFC-21272183, 21002077), and the Fund of the Rising Stars of Shanxi Province (2012KJXX-26).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307942.

Table 1: Reaction optimization for the palladium-catalyzed carbonylation of the alkenyl C—H bond of enamide.[a]

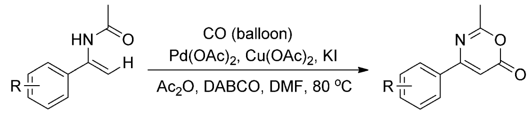


1a **2a**

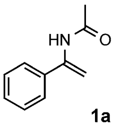
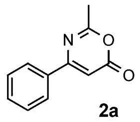
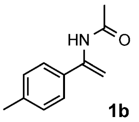
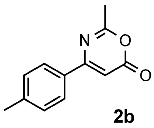
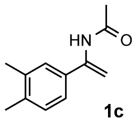
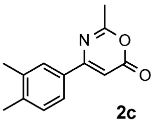
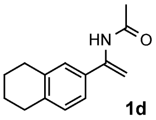
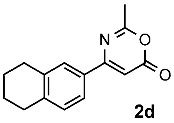
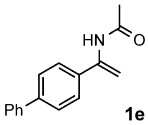
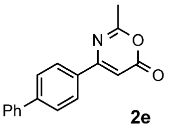
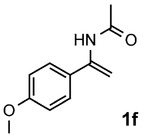
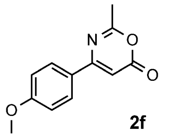
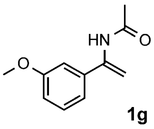
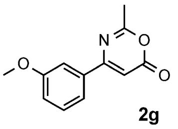
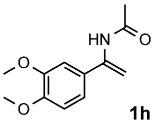
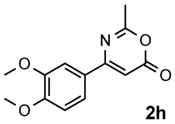
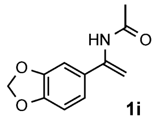
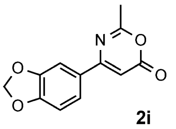
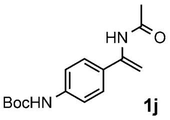
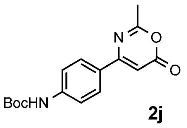
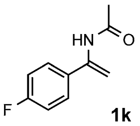
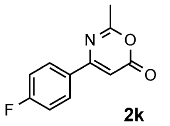
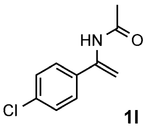
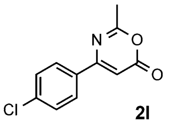
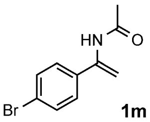
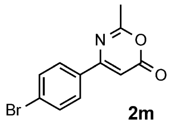
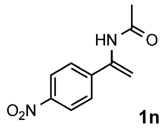
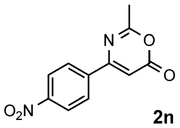
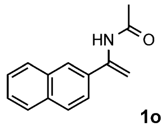
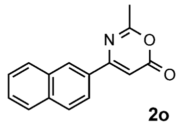
Entry	Additive	Base	Solvent	Yield [%][b]
1	–	–	DMF	12
2	KI	–	DMF	25
3	KI	–	CH_3CN	9
4	KI	–	toluene	8
5	KI	–	THF	18
6[c]	KI	–	DMF	35
7[c,d]	KI, Ac_2O	–	DMF	45
8[c,d]	KI, Ac_2O	KOAc	DMF	56
9[c,d]	KI, Ac_2O	K_2CO_3	DMF	38
10[c,d]	KI, Ac_2O	*t*BuOK	DMF	48
11[c,d]	KI, Ac_2O	NEt_3	DMF	50
12[c,d]	KI, Ac_2O	DABCO	DMF	84

[a] Reaction conditions: enamide **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv), KI (0.2 equiv), base (1.5 equiv), solvent (2 mL), CO (balloon pressure), at 80°C. [b] Yield of isolated product. [c] KI (1.0 equiv). [d] Ac_2O (3.0 equiv). THF = tetrahydrofruan.

Table 2: Palladium-catalyzed carbonylation of the alkenyl C—H bond of enamides for the synthesis of 1,3-oxazin-6-ones.[a]



1 **2**

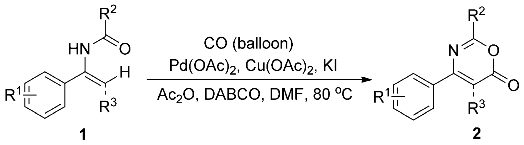
Entry	Substrate	Product	Yield [%][b]
1	 **1a**	 **2a**	84
2	 **1b**	 **2b**	86
3	 **1c**	 **2c**	80
4	 **1d**	 **2d**	95
5	 **1e**	 **2e**	86
6	 **1f**	 **2f**	89
7	 **1g**	 **2g**	73
8	 **1h**	 **2h**	78
9	 **1i**	 **2i**	81
10	 **1j**	 **2j**	74
11	 **1k**	 **2k**	88
12	 **1l**	 **2l**	79
13	 **1m**	 **2m**	70
14	 **1n**	 **2n**	40
15	 **1o**	 **2o**	83

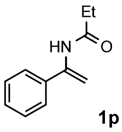
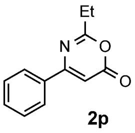
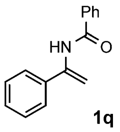
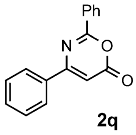
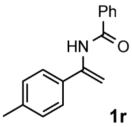
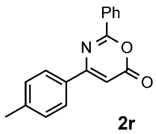
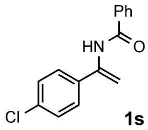
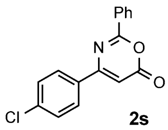
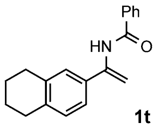
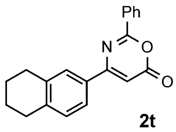
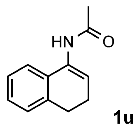
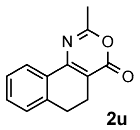
[a] Reaction conditions: enamide **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1.0 equiv), KI (1.0 equiv), Ac_2O (3.0 equiv), DABCO (1.5 equiv), DMF (2 mL), CO (balloon pressure), 80°C. [b] Yield of isolated product. Boc = *tert*-butoxycaarbonyl.

ing substituted 1,3-oxazin-6-ones in high to excellent yields. Electron-neutral substituents, such as methyl, alkyl, phenyl, on the aromatic ring of the enamides give the best results with up to 95% yield of the 1,3-oxazin-6-one product under the standard conditions (Table 2, entries 1–5). Enamides substituted with electron-donating groups, such as methoxyl, [1,3]dioxole, and amino, or electron-withdrawing groups such as chloro and bromo, reacted smoothly and resulted in the carbonylation products **2f–m** in 70–89% yields, thus implying that the electronic nature of the substrates has little influence on the carbonylation reaction (Table 2, entries 6–13). However, the strong electron-poor nitro-substituted **2n** was only obtained in 40% yield, with 52% recovery of the enamide **1n** (Table 2, entry 14). In addition, the β-naphthyl-substituted enamide **1o** shows reactivity similar to that of the aryl-substituted enamides and afforded the corresponding **2o** in 83% yield (Table 2, entry 15).

Furthermore, *N*-propionyl and *N*-benzoyl enamides (**1p–t**) were investigated to explore the reaction scope (Table 3). The carbonylation reactions proceeded smoothly to give the corresponding 2-ethyl and 2-phenyl 1,3-oxazin-6-ones **2p–t** in good yields. These results indicated that a variety of 2-substituted 1,3-oxazin-6-ones could be prepared by this carbonylation reaction. However, β-substituted enamides were unable to induce the carbonylation reaction, for example, *N*-(3,4-dihydronaphthalen-1-yl)acetamide (**1u**) gave only trace amounts of the desired product **2u**, and **1u** was mostly recovered (Table 3, entry 6).

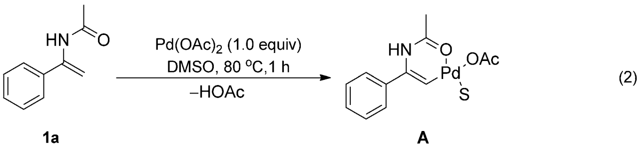
Table 3: Palladium-catalyzed carbonylation of the alkenyl C−H bond of enamides for the synthesis of 1,3-oxazin-6-ones.[a]



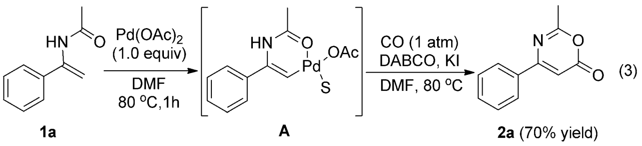
Entry	Substrate	Product	Yield [%][b]
1	 **1p**	 **2p**	61
2	 **1q**	 **2q**	83
3	 **1r**	 **2r**	87
4	 **1s**	 **2s**	66
5	 **1t**	 **2t**	85
6	 **1u**	 **2u**	<5

[a] Reaction conditions: enamide **1** (0.2 mmol), Pd(OAc)$_2$ (5 mol%), Cu(OAc)$_2$ (1.0 equiv), KI (1.0 equiv), Ac$_2$O (3.0 equiv), DABCO (1.5 equiv), DMF (2 mL), CO (balloon pressure), 80°C. [b] Yield of isolated product.

To gain more insight into the mechanism of the reaction, **1a** was reacted with a stoichiometric amount of palladium acetate in [D$_6$]DMSO. A palladium complex, whose structure is consistent with **A** by ^{1}H NMR and high-resolution mass spectrometry analysis, was obtained in nearly quantitative yield [Eq. (2); DMSO = dimethylsulfoxide; S in structure **A** stands for solvent].[15] Loh and co-workers had recently characterized the same six-membered vinylpalladium complex.[8b] Our data is in agreement with the results reported by Loh and co-workers.

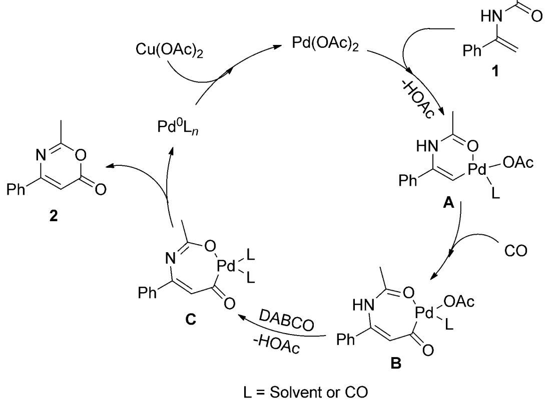


Then, the stoichiometric reaction was performed in DMF which was optimized solvent for the carbonylation reaction [Eq. (3)].[15] Treating the vinylpalladium complex **A** with



DABCO in the presence of KI in DMF under a CO atmosphere gave the **2a** in 70% yield. Therefore, the vinylpalladium complex **A**, which was generated from alkenyl C−H bond cleavage, should be a key intermediate in the carbonylation reaction.

On the basis of the above results and previous studies, a tentative mechanism for this carbonylation is proposed in Scheme 1. Alkenyl C−H activation by Pd(OAc)$_2$ forms the



Scheme 1. A plausible mechanism for palladium-catalyzed carbonylation of enamides.

vinylpalladium intermediate **A**.[8a–b,16] Coordination and insertion of CO into **A** affords the acylpalladium intermediate **B**. Then, **B** is transformed into **C** assisted by DABCO. Reductive elimination of **C** gives the carbonylation product 1,3-oxazin-6-one **2** and Pd^0. Finally, Pd^0 is reoxidized by Cu(OAc)$_2$ to regenerate the Pd(OAc)$_2$ catalyst.

In summary, we have developed the first palladium-catalyzed carbonylation of alkenyl C–H bonds of enamides with CO for the synthesis of 1,3-oxazin-6-ones. The reaction employs KI and Ac$_2$O as additives and proceeds under mild basic conditions. This novel palladium-catalyzed carbonylation reaction tolerates a wide range of functional groups and is a reliable method for the rapid elaboration of readily available enamides into a variety of substituted 1,3-oxazin-6-ones under atomospheric pressure of CO. Further studies on substrate scope and mechanism of the reaction are underway in our laboratory and will be reported in due course.

Experimental Section

Enamides **1** (0.2 mmol), Pd(OAc)$_2$ (5 mol%, 2.2 mg), Cu(OAc)$_2$ (0.2 mmol, 36.3 mg), KI (0.2 mmol, 33.2 mg), Ac$_2$O (0.6 mmol, 61.2 mg), DABCO (0.3 mmol, 33.6 mg), and DMF (2 mL) was charged in a 10 mL round-bottom flask. The flask was then, evacuated and back-filled with CO (3-times, balloon) and stirred at 80 °C. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature and vented to discharge the excess CO. The reaction was quenched with H$_2$O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and then evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding 1,3-oxazin-6-one **2** with hexanes/ethyl acetate as the eluent.

Received: September 10, 2013

Keywords: C–H activation · carbonylation · heterocycles · heterogeneous catalysis · palladium

---

[1] a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1; b) Q. Liu, H. Zhang, A. Lei, *Angew. Chem.* **2011**, *123*, 10978; *Angew. Chem. Int. Ed.* **2011**, *50*, 10788.

[2] a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114; c) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 7474; *Angew. Chem. Int. Ed.* **2010**, *49*, 7316; d) H. Zhang, R. Shi, A. Ding, L. Lu, B. Chen, A. Lei, *Angew. Chem.* **2012**, *124*, 12710; *Angew. Chem. Int. Ed.* **2012**, *51*, 12542.

[3] a) R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675; b) F. Hebrard, P. Kalck, *Chem. Rev.* **2009**, *109*, 4272.

[4] a) J. R. Zoeller, V. H. Agreda, S. L. Cook, N. L. Lafferty, S. W. Polichnowski, D. M. Pond, *Catal. Today* **1992**, *13*, 73; b) J. F. Roth, J. H. Craddock, A. Hershman, F. E. Paulik, *Chem. Tech.* **1971**, *1*, 600.

[5] a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; b) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; c) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293; d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; e) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; f) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879.

[6] a) N. Chatani, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1996**, *118*, 493; b) T. Fukuyama, N. Chatani, J. Tatsumi, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1998**, *120*, 11522; c) N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882; d) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898; e) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 8070.

[7] a) Z.-H. Guan, M. Chen, Z.-H. Ren, *J. Am. Chem. Soc.* **2012**, *134*, 17490; b) Z.-H. Guan, Z.-H. Ren, S. M. Spinella, S. Yu, Y.-M. Liang, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 729; c) R. Giri, J. K. Lam, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 686; d) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagne, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 1862; *Angew. Chem. Int. Ed.* **2009**, *48*, 1830; e) Y. Lu, D. Leow, X. Wang, K. M. Engle, J.-Q. Yu, *Chem. Sci.* **2011**, *2*, 967; f) R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14082; g) B. Haffemayer, M. Guliasa, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 312; h) H. Zhang, R. Shi, P. Gan, C. Liu, A. Ding, Q. Wang, A. Lei, *Angew. Chem.* **2012**, *124*, 5294; *Angew. Chem. Int. Ed.* **2012**, *51*, 5204; i) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, M. Tokuda, *J. Am. Chem. Soc.* **2004**, *126*, 14342; j) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 9902; k) S. Luo, F.-X. Luo, X.-S. Zhang, Z.-J. Shi, *Angew. Chem.* **2013**, *125*, 10792; *Angew. Chem. Int. Ed.* **2013**, *52*, 10598; l) D. Liang, Z. Hu, J. Peng, J. Huang, Q. Zhu, *Chem. Commun.* **2013**, *49*, 173; m) Q. Xing, L. Shi, R. Lang, C. Xia, F. Li, *Chem. Commun.* **2012**, *48*, 11023.

[8] a) K. Sasano, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2013**, *135*, 10954; b) Y.-H. Xu, Y. K. Chok, T.-P. Loh, *Chem. Sci.* **2011**, *2*, 1822; c) C. Feng, T.-P. Loh, *Chem. Sci.* **2012**, *3*, 3458; d) H. Chen, C. Cai, X. Liu, X. Li, H. Jiang, *Chem. Commun.* **2011**, *47*, 12224.

[9] For the synthesis of enamides, see: Z.-H. Guan, Z.-Y. Zhang, Z.-H. Ren, Y.-Y. Wang, X. Zhang, *J. Org. Chem.* **2011**, *76*, 339.

[10] a) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713; b) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111*, 4599; c) R. Matsubara, S. Kobayashi, *Acc. Chem. Res.* **2008**, *41*, 292; d) W. Zhang, Y. Chi, X. Zhang, *Acc. Chem. Res.* **2007**, *40*, 1278.

[11] a) S. Pankajakshan, Y.-H. Xu, J. K. Cheng, M. T. Low, T.-P. Loh, *Angew. Chem.* **2012**, *124*, 5799; *Angew. Chem. Int. Ed.* **2012**, *51*, 5701; b) H. Zhou, Y.-H. Xu, W.-J. Chung, T.-P. Loh, *Angew. Chem.* **2009**, *121*, 5459; *Angew. Chem. Int. Ed.* **2009**, *48*, 5355; c) H. Zhou, W.-J. Chung, Y.-H. Xu, T.-P. Loh, *Chem. Commun.* **2009**, 3472; d) K. D. Hesp, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *133*, 11430; e) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; f) L. Wang, L. Ackermann, *Org. Lett.* **2013**, *15*, 176; g) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Chem. Commun.* **2012**, *48*, 8105.

[12] a) J. Dupont, C. S. Consorti, J. Spenser, *Chem. Rev.* **2005**, *105*, 2527; b) A. D. Ryabov, *Synthesis* **1985**, 233; c) H. Horino, N. Inoue, *J. Org. Chem.* **1981**, *46*, 4416.

[13] a) F. Risitano, G. Grassi, F. Foti, F. Caruso, G. L. Vecchio, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1522; b) Y. Yamamoto, Y. Morita, K. Minami, *Chem. Pharm. Bull.* **1986**, *34*, 1980.

[14] a) Z.-H. Guan, H. Lei, M. Chen, Z.-H. Ren, Y. Bai, Y.-Y. Wang, *Adv. Synth. Catal.* **2012**, *354*, 489; b) S. Fukuoka, M. Chono, M. Kohno, *J. Org. Chem.* **1984**, *49*, 1458; c) V. L. K. Valli, H. Alper, *Organometallics* **1995**, *14*, 80.

[15] See the Supporting Information for details.

[16] G. R. Newkome, K. J. Theriot, B. K. Cheskin, D. W. Evans, G. R. Baker, *Organometallics* **1990**, *9*, 1375.