

Biaryl Formation from 5-(2-Bromobenzyl)-Substituted Piperidin-2-ones via Palladacycles

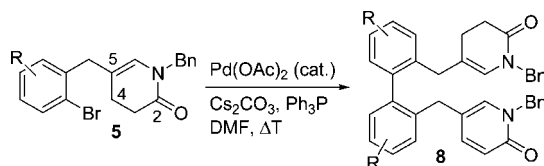
Gedu Satyanarayana and Martin E. Maier*

Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18,
72076 Tübingen, Germany

martin.e.maier@uni-tuebingen.de

Received February 13, 2008

ABSTRACT



The reaction of piperidin-2-ones with a 2-bromobenzyl substituent in the 5-position in the presence of a palladium catalyst leads to biaryl compounds. Their formation can be explained via initial C–H insertion of the aryl palladium species into the allylic C–H bond of the piperidinone. This eventually leads to a metallacycle containing Pd(II) that inserts another aryl bromide, promoting the formation of the biaryl bond.

Transition-metal catalysis allows transformations on organic substrates that are otherwise not possible or difficult to achieve. One of the prominent metals in this regard is palladium which is used for hydrogenations and cross-coupling reactions. Some classical cross-coupling reactions mediated by palladium are the Heck,¹ Stille,² Suzuki,³ and Sonogashira⁴ coupling. Furthermore, in recent years, C–H insertion reactions via organopalladium intermediates have enriched the repertoire of methods for organic synthesis. The Heck reaction is characterized by the insertion of an alkene into a Pd–C bond. Commonly, alkenes with an electron-

withdrawing substituent are used in a Heck reaction.^{5,6} However, terminal alkenes or even electron-rich alkenes, such as enol ethers and enamides, have been employed as well. Generally, enamides undergo coupling with the carbon next to the nitrogen atom with an organopalladium species. In connection with the synthesis of annulated ring systems, we planned to implement an intramolecular Heck reaction on an aryl bromide of type **A** (Scheme 1). Accordingly, insertion^{7–9} of the enamide double bond into the aryl–Pd bond of **B** should eventually lead to **D** or a double-bond isomer thereof. However, the expected products such as **D** were not observed. In this paper, we show that 5-(2-bromobenzyl)-

(1) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (b) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989. (c) Link, J. T. *Org. React.* **2002**, *60*, 157–534.

(2) (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652. (b) Duncanson, M. A. J.; Pattenden, G. J. *Chem. Soc., Perkin Trans. I* **1999**, 1235–1246. (c) Gonthier, E.; Breinbauer, R. *Molecular Diversity* **2005**, *9*, 51–62. (d) Echavarren, A. M. *Angew. Chem.* **2005**, *117*, 4028–4031; *Angew. Chem., Int. Ed.* **2005**, *44*, 3962–3965.

(3) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem.* **2001**, *113*, 4676–4701; *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568. (c) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313–4327. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440. (e) Suzuki, A. *Chem. Commun.* **2005**, 4759–4763. (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem.* **2005**, *117*, 4516–4563; *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489. (g) Kantechev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Aldrichim. Acta* **2006**, *39*, 97–111.

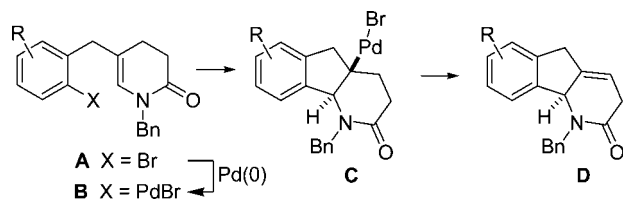
(4) (a) Doucet, H.; Hierro, J.-C. *Angew. Chem.* **2007**, *119*, 850–888; *Angew. Chem., Int. Ed.* **2007**, *46*, 834–871. (b) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874–922. (c) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108.

(5) (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (b) Dunina, V. V.; Gorunova, O. N. *Russ. Chem. Rev.* **2004**, *73*, 309–350. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72.

(6) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727–2734.

(7) (a) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639–6645. (b) Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277–9280. (c) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212–5218. (d) Mo, J.; Liu, S.; Xiao, J. *Tetrahedron* **2005**, *61*, 9902–9907. (e) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751–760.

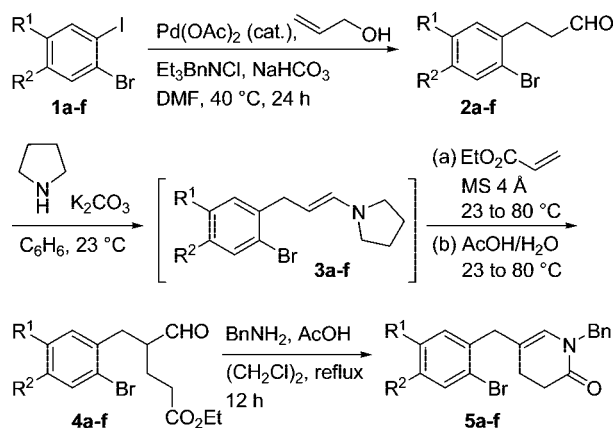
Scheme 1. Intended Annulation Reaction Using Cyclic Enamides



substituted-3,4-dihydro-2(1H)-pyridinones, which contain a cyclic enamide function, enter into a completely different pathway in presence of a palladium catalyst.

The required substrates were easily prepared from bromiodobenzenes^{10–13} **1a–f** (Scheme 2, Table 1). Via

Scheme 2. Synthesis of the Cyclic Enamides **5a–f** via Heck Coupling, Michael Addition of the Enamines **3a–f** to Ethyl Acrylate and Cyclization of the 4-Formyl Esters **4a–f** with Benzylamine



Jeffery–Heck coupling¹⁴ with allyl alcohol, these aryl iodides were extended to 3-(2-bromo)phenylpropanals **2a–f**. The obtained aldehydes **2a–f** were then converted to the corresponding enamines using pyrrolidine in presence of K₂CO₃. Treatment of the crude enamines with ethyl acrylate followed by acidic workup furnished the 4-formyl esters **4a–f**.¹⁵ These modified conditions are a significant improvement over the previously reported ones. As shown previ-

Table 1. Yields for the Transformations Leading to Piperidinones **5a–f**

R ¹	R ²	coupling step (%)	Michael addition (%)	cyclization to enamide (%)
H	H	2a (80)	4a (75)	5a (85)
H	Me	2b (70)	4b (72)	5b (78)
H	CO ₂ Me	2c (75)	4c (72)	5c (79)
OMe	H	2d (70)	4d (73)	5d (83)
OMe	OMe	2e (70)	4e (73)	5e (85)
H	OMe	2f (74)	4f (64)	5f (89)

ously,¹⁶ the 4-formyl esters provide piperidinones by reductive amination with benzylamine and sodium cyanoborohydride. If the less powerful reducing agent sodium triacetoxy borohydride was employed, the piperidinones were accompanied by the cyclic enamide. If the reducing agent was omitted and the formyl esters were simply reacted with benzylamine in refluxing dichloroethane, the cyclic enamides **5a–f** were the sole product. The yields for the individual steps of the sequence shown in Scheme 2 are listed in Table 1.

In an attempt to perform a palladium-catalyzed ring annulation reaction, the 5-(2-bromobenzyl)-substituted pyridinone **5a** was stirred with Pd(OAc)₂ (0.1 equiv), Ph₃P (0.2 equiv), and Cs₂CO₃ (4 equiv) in hot DMF (Table 2, entry 1). After 24 h, some starting material was left, but two new compounds **7a** and **8a** were isolated. The base K₂CO₃ gave almost the same results (25% **5a**, 21% **7a**, 41% **8a**). Longer reaction times (entry 2) also produced some of the debrominated pyridinone **6a**. The highest yield for the biaryl compound **8a** was obtained by running the reaction at higher temperature for 48 h (entry 3). Comparable ratios of the three compounds **6a–8a** were obtained using HMPA as solvent (entry 4). Using binap as ligand, and K₂CO₃ as base, the amount of the simple debromination product **6a** increased at the expense of **7a** and **8a** (entry 5). The sterically hindered and electronrich Buchwald phosphine ligand *N*-[2'-(dicyclohexylphosphino)-1,1'-biphenyl-2-yl]-*N,N*-dimethylamine (davephos) also favored the debrominated compound **6a** (entry 6). Among the dipolar solvents, DMF turned out to be the best one. In DMSO, the formation of the biaryl compound is suppressed with the 1,5-dibenzyl-2(1H)-pyridinone (**7a**) being the major product (entry 7). The palladium source may also be varied without significant changes in the product ratios as illustrated with entries 8 and 9.

The formation of pyridin-2(1H)-one **7a** and the biphenyl-substituted pyridinone **8a** can only be explained by C–H insertion of the arylpalladium species **E** into the allylic C–H bond, yielding palladacycle **F** (Scheme 3). Via elimination of

(8) (a) For some intramolecular Heck reactions of enamide containing substrates, see: Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595–602. (b) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716–1724. (c) Arthuis, M.; Pontikis, R.; Florent, J.-C. *Tetrahedron Lett.* **2007**, *48*, 6397–6400.

(9) For the Heck reaction using pyrroles, see: Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529.

(10) (a) Compound **1b**: Bard, R. R.; Bunnett, J. F.; Traber, R. P. *J. Org. Chem.* **1979**, *44*, 4918–4924. (b) van Klink, G. P. M.; de Boer, H. J. R.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F.; Spek, A. L. *Organometallics* **2002**, *21*, 2119–2135.

(11) Compound **1c**: Vu, C. B.; Corpuz, E. G.; Merry, T. J.; Pradeepan, S. G.; Bartlett, C.; Bohacek, R. S.; Botfield, M. C.; Eyermann, C. J.; Lynch, B. A.; MacNeil, I. A.; Ram, M. K.; van Schravendijk, M. R.; Violette, S.; Sawyer, T. K. *J. Med. Chem.* **1999**, *42*, 4088–4098.

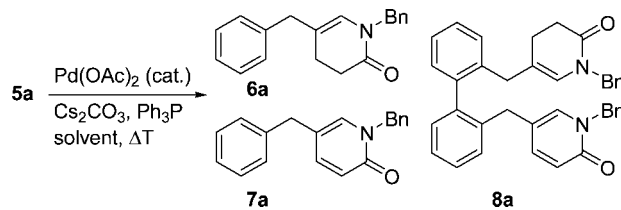
(12) Compound **1d**: Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206.

(13) Compound **1e**, **1f**: Orito, K.; Hatakeyama, T.; Takeo, M.; Sugimoto, H. *Synthesis* **1995**, *127*, 3–1277.

(14) (a) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121–2124. (b) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546. (c) Tietze, L. F.; Kahle, K.; Raschke, T. *Chem. Eur. J.* **2002**, *8*, 401–407. (d) Bruyère, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007–4017.

(15) Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78–87.

Table 2. Reaction of the Piperidinone **5a** with Pd(OAc)₂, Base, and Ph₃P under Various Conditions

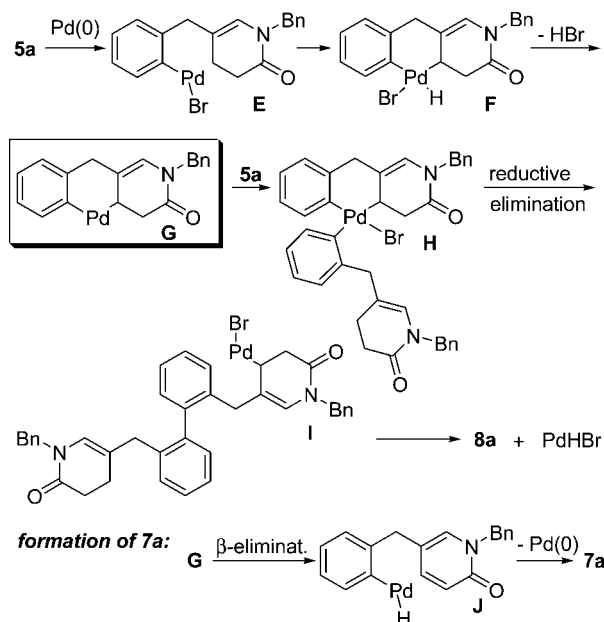


entry	solvent	<i>T</i> (°C)	time (h)	6a (%)	7a (%)	8a (%)
1 ^a	DMF	100	12		24	43
2 ^b	DMF	100	24	17	20	42
3	DMF	120	48	10	30	48
4	HMPA	140	48	15	21	47
5 ^c	DMF	120	48	24	15	16
6 ^d	DMF	120	48	25	16	28
7	DMSO	120	48	23	26	9
8 ^e	DMF	120	48	12	28	46
9 ^f	DMF	120	48	14	24	42

^a Recovered starting material = 25%. ^b Recovered starting material = 7%. ^c binap (0.15 equiv) was used as ligand. ^d *N*-[2'-(Dicyclohexylphosphino)-1,1'-biphenyl-2-yl]-*N,N*-dimethylamine (0.2 equiv) was used as ligand. ^e Pd(PPh₃)₂Cl₂ (10 mol %) as catalyst, without additional Ph₃P. ^f Pd(PPh₃)₄ (10 mol %).

H–Br the reactive palladium species **G** might form.¹⁷ The key palladacycle **G** could undergo insertion into the C–Br bond of a second molecule of **5a** leading to the Pd(IV) complex **H**.^{18,19} Reductive elimination should lead to formation of the biaryl bond providing intermediate **I**. Elimination of PdHBr would complete the catalytic cycle. As another option, palladacycle

Scheme 3. Proposed Mechanisms Explaining the Formation of **6a–8a**^a



^aFor simplicity, phosphine ligands are omitted.

G could undergo a β -elimination to give the palladium hydride **J**. Expulsion of Pd(0) would lead to the pyridin-2(1*H*)-one **7a**. Formation of the pyridin-2(1*H*)-one **7a** could also occur via reductive elimination from **F** followed by elimination of PdHBr from the pyridinone intermediate.

The mechanism suggested in Scheme 3 is reminiscent of the classical Catellani process where an initial arylpalladium species inserts norbornene which allows a subsequent formal C–H insertion to produce a palladacycle [Pd(II)] that is ready for further coupling reactions.^{20–24}

In all, the conditions found in entry 3 of Table 2 turned out to be the best with regard to the yield of biaryl compound **8a**. Therefore, these conditions were applied to the other enamides **5b–f** from Scheme 1. Thus, the enamides were reacted in presence of Pd(OAc)₂ (0.1 equiv), PPh₃ (0.2 equiv), and Cs₂CO₃ (4 equiv) in DMF for 48 h at 100 or 120 °C. As can be seen from Table 3, the biaryl derivatives **8** were formed in yields ranging from 35–48%. With the byproducts **6** and **7** taken into consideration the mass balance is quite good. The pyridine derivatives **7** show a characteristic doublet (3-*H*) at around 6.5 ppm. In the dimers **8**, the corresponding signal (*J* = 9.4 Hz) appears at slightly higher field, typically at around 6.4 ppm. In all cases of Table 3, the crude reaction mixture contains some triphenylphosphine oxide as an impurity. For entries 3 and 5 (**8c** and **8e**) it is easily removed during chromatography. With biaryls **8a** and **8b** this separation is more difficult. However, for these compounds the Buchwald ligand *N*-[2'-(dicyclohexylphosphino)-1,1'-biphenyl-2-yl]-*N,N*-dimethylamine (0.2 equiv) may be used instead of Ph₃P. Then the biaryl compounds can be separated from phosphine oxide impurities, even though the yields are slightly lower. For entries 4 and 6 (**8d** and **8f**), the Ph₃P=O impurity can be removed almost completely. In these cases, the impurity from the Buchwald ligand coelutes with the biaryl products.

The insertion of the palladium (cf. **E**, Scheme 3) into the allylic C–H bond of the pyridinone ring only seems to occur due to the lack of other reagents (Scheme 4). In a control experiment, the reaction of aryl bromide **5b** was run under identical conditions (see Table 3) but with added ethyl acrylate (2 equiv). In this case, the normal Heck product **9** turned out to be the major product (48%) along with some debrominated **6b** (25%).

In summary, we could demonstrate the facile synthesis of 5-substituted 3,4-dihydro-1*H*-pyridin-2-ones from easily ac-

(16) Satyanarayana, G.; Maier, M. E. *Tetrahedron* **2008**, *64*, 356–363.

(17) For a review about palladacycles, see: Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2571.

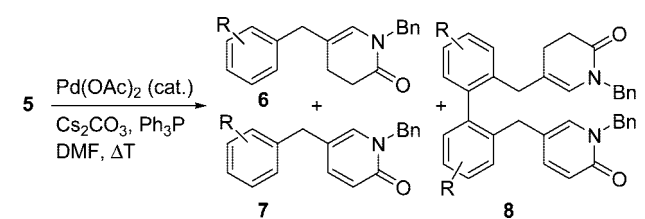
(18) (a) For the chemistry of Pd(IV) complexes, see: Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83–90. (b) Canty, A. J.; Hoare, J. L.; Davies, N. W.; Traill, P. R. *Organometallics* **1998**, *17*, 2046–2051.

(19) For an alternative, see: Cardenas, D. J.; Martin-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033–5040.

(20) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem.* **1997**, *109*, 142–145; *Angew. Chem., Int. Ed.* **1997**, *36*, 119–122. (b) Catellani, M.; Cugini, F. *Tetrahedron* **1999**, *55*, 6595–6602. (c) Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157–158. (d) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78–79.

(21) (a) For reviews, see: Catellani, M. *Synlett* **2003**, 298–313. (b) Catellani, M.; Motti, E.; Della Ca, N.; Ferraccioli, R. *Eur. J. Org. Chem.* **2007**, 4153–4165. (c) Johnson, J. B.; Rovis, T. *Angew. Chem.* **2008**, *120*, 852–884; *Angew. Chem., Int. Ed.* **2008**, *47*, 840–871.

Table 3. Palladium-Catalyzed Transformation of the 5-(2-Bromobenzyl)-substituted-3,4-dihydro-2(1*H*)-pyridinones **5a–f**^a

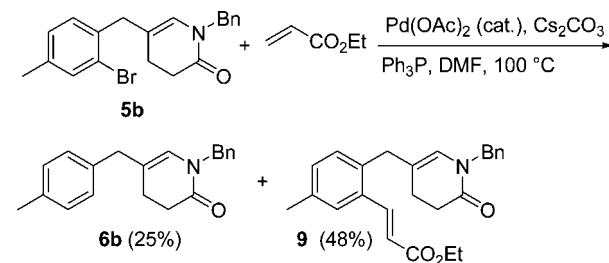


entry	5	6 (%)	7 (%)	8 [%]	(%)
1	5a	6a (10)	7a (30)		48
2	5b	6b (12)	7b (28)		46
3 ^b	5c	6c (15)	7c (28)		36
4 ^c	5d	6d (16)	7d (27)		41
5 ^c	5e	6e (16)	7e (27)		35
6	5f	6f (13)	7f (26)		44

^a Reaction conditions: Pd(OAc)₂ (0.1 equiv), PPh₃ (0.2 equiv), Cs₂CO₃ (4 equiv), DMF (0.18–0.2 M), 120 °C, 48 h. ^b K₂CO₃ (4 equiv) was used as base; with Cs₂CO₃ the yields were 9% (**6c**), 21% (**7c**), 23% (**8c**). ^c Temperature = 100 °C.

cessible 4-formyl esters with a 2-bromophenyl group at the terminus. These enamides enter into a novel reaction pathway

Scheme 4. Classical Heck Coupling of Aryl Bromide **5b** with Ethyl Acrylate



in presence of a palladium catalyst. Thus, with the 2-bromobenzyl substituent, the arylpalladium species undergoes a C–H insertion reaction to a palladium intermediate, which can react with another arylbromide leading to biaryl compounds such as **8a**. This sequence is unprecedented and further illustrates the power of transition metal catalyzed reactions. In fact, biaryl compounds are of great importance in many areas of chemistry.²⁵ Thus, chiral biaryls function as efficient ligands in asymmetric synthesis.²⁶ In addition, the biaryl subunit can be found in many natural products, like alkaloids or unusual peptide-based compounds.²⁷ Moreover, biaryl compounds are widely used in material science²⁸ and medicinal chemistry.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Graeme Nicholson (Institute of Organic Chemistry) for measuring the HRMS spectra. G.S. thanks the Alexander von Humboldt foundation for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL800330D

(22) (a) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127–8134. (b) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827–4830. (c) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149. (d) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436–14437. (e) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255–5258. (f) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem.* **2007**, *119*, 1507–1510; *Angew. Chem., Int. Ed.* **2007**, *46*, 1485–1488. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.

(23) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115–3118.

(24) (a) Dyker, G. *Chem. Ber./Recl.* **1997**, *130*, 1567–1578. (b) Dyker, G. *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem., Int. Ed.* **1999**, *38*, 1699–1712.

(25) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.

(26) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–897.

(27) Feliu, L.; Planas, M. *Int. J. Pept. Res. Ther.* **2005**, *11*, 53–97.

(28) Kandre, R.; Feldman, K.; Meijer, H. E. H.; Smith, P.; Schlüter, A. D. *Angew. Chem.* **2007**, *119*, 5044–5047; *Angew. Chem., Int. Ed.* **2007**, *46*, 4956–4959.