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Bispalladacycle-Catalyzed Brønsted Acid/Base-Promoted Asymmetric Tandem Azlactone Formation−Michael Addition

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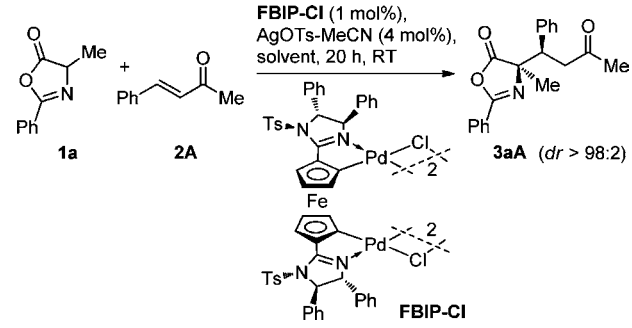
Abstract: Cooperative activation by a soft bimetallic catalyst, a hard Brønsted acid, and a hard Brønsted base has allowed the formation of highly enantioenriched, diastereomerically pure masked α-amino acids with adjacent quaternary and tertiary stereocenters in a single reaction starting from racemic N-benzoylated amino acids. The products can, for example, be used to prepare bicyclic dipeptides.

The catalytic asymmetric construction of quaternary stereocenters has been intensively studied in the past decade and has reached a high level of productivity for various reaction types.[1] In contrast, for the simultaneous formation of adjacent quaternary and tertiary stereocenters, only a limited number of highly diastereo- and enantioselective protocols are available.[1] Among those, direct conjugate additions of α-carbonyl-stabilized nucleophiles to activated olefins[2] are very attractive for C−C bond constructions because of their atom economy and the versatility of the activating functional groups.[3] The step economy can be further increased by the development of tandem processes, thus allowing the construction of stereochemically complex and densely functionalized building blocks employing simple starting materials.[4] We present herein a tandem process in which racemic N-benzoylated amino acids are transformed in situ into azlactones [oxazol-5-(4*H*)-ones] that undergo an enantio- and diastereoselective Michael addition to enones triggered by a planar chiral bispalladacycle.

Azlactones in their role as masked and activated amino acid fragments have recently been studied in different types of (organo)catalytic asymmetric reactions.[5−11] Their use is particularly attractive for diversity-oriented synthesis because of the presence of orthogonal nucleophilic and electrophilic reactive sites. Organocatalytic 1,4-additions of azlactones to enals using proline-derived organocatalysts have been reported to proceed with moderate to good diastereoselectivity and high enantioselectivity.[12,13] Moreover, organocatalytic protocols have lately been developed for highly reactive Michael acceptors,[14−18] whereas the use of the less electrophilic enones has not been reported before.

We recently showed that the bispalladacycle **FBIP-Cl**[19−21] is able to catalyze the asymmetric Michael addition of α-cyanoacetates to vinyl ketones, generating a quaternary stereocenter.[22] A bimetallic activation mode[23] had received validation by spectroscopic and kinetic investigations. Utilizing similar reaction conditions for the addition of azlactone **1a** to β-substituted enone **2A** (diglyme, room temperature, activation of **FBIP-Cl** with AgOTs for chloride exchange by the less Lewis basic tosylate) resulted in low enantioselectivity (39% ee) and poor yield (3%; Table 1, entry 1).[24] Using dichloromethane as the solvent resulted in more product formation but poor enantioselectivity (entry 2), which could be improved by using acetic acid as an additive (entry 3). However, much higher enantioselectivity was attained in pure acetic acid,

Table 1. Investigation of the Solvent Effect



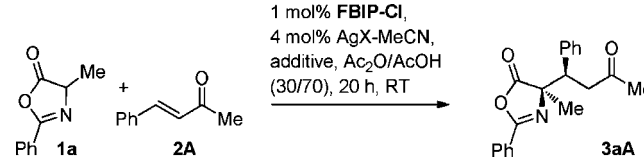
entry	solvent	conv. (%)[a]	yield (%)[a]	ee (%)[b]
1	diglyme	16	3	39
2	CH_2Cl_2	56	25	17
3	CH_2Cl_2 + 0.3 equiv of HOAc	64	21	39
4	HOAc	83	47	73
5	HOAc + 30 vol % Ac_2O	90	46	79

[a] Determined by ^{1}H NMR analysis using mesitylene as an internal standard. [b] Determined by HPLC.

which also had a positive impact on the product yield (entry 4). With acetic anhydride as the cosolvent (30 vol %), similar reactivity with slightly improved enantioselectivity was observed (entry 5).

Various silver salts were subsequently evaluated for catalyst activation (Table 2). AgOTs (entry 1) and AgOTf (entry 2) gave similar results (79 and 78% ee, respectively). Catalysts with a carboxylate or the noncoordinating BF_4^- counterion performed slightly less well in terms of enantioselectivity (entries 3−5).

Table 2. Investigation of the Catalyst Activation



entry	AgX	additive (mol %)	conv. (%)[a]	yield (%)[a]	dr[a]	ee (%)[b]
1	AgOTs	−	90	46	>98:2	79
2	AgOTf	−	72	37	96:4	78
3	AgOAc	−	50	44	>98:2	70
4	AgO_2CCF_3	−	58	50	>98:2	72
5	$AgBF_4$	−	60	26	>98:2	74
6	AgOTs	NaOAc (4)	94	83	>98:2	78
7	AgOTf	NaOAc (4)	89	85	>98:2	78
8	AgOAc	NaOAc (4)	100	73	>98:2	78
9[c]	**AgOTf**	**NaOAc (10)**	**100**	**98**	**>98:2**	**79**
10	−	NaOAc (4)	40	8	>98:2	31

[a] Determined by ^{1}H NMR analysis using mesitylene as an internal standard. [b] Determined by HPLC. [c] The reaction used 2 mol % **FBIP-Cl** and 8 mol % AgOTf and was performed at 30 °C with 2 equiv of **2A**.

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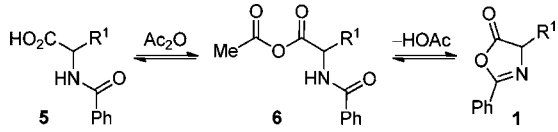
An improvement of the product yield was achieved by addition of catalytic amounts of NaOAc (entries 6−9). In contrast, poor results were obtained in the presence of NaOAc when the catalyst was not activated by a silver salt (entry 10).

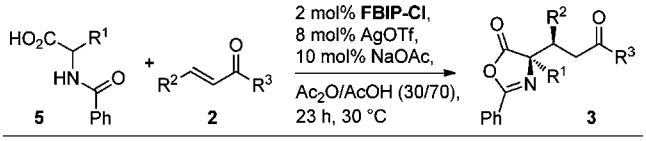
Since the activated catalyst is stable toward acetic anhydride, the in situ formation of azlactones by O-acylation of N-benzoylated amino acids **5**, generating mixed anhydrides **6** as intermediates, was envisaged (Scheme 1).

Scheme 1. In Situ Azlactone Formation



Application of the reaction conditions optimized for the conjugate addition of preformed azlactone **1a** (see Table 2, entry 9) to a tandem process (Table 3) resulted in an excellent yield and diastereoselectivity for the formation of **3aA** starting from racemic *N*-benzoylalanine (**5a**), and the enantioselectivity was only slightly affected (Table 3, entry 1). Changing the substituent R^1 at the enolizable α-C atom to a substituent with larger steric demand than Me generally resulted in higher enantioselectivity (entries 2−16) of up to 99% ee (entry 11). For the enone substituents R^2 and R^3, the combinations aryl/alkyl (entries 1−5, 8−13, and 16), alkyl/alkyl (entries 6, 7, and 15) and aryl/aryl (entry 14) were all well-tolerated and provided good yields and high stereoselectivities. Examination of various functional groups on aromatic R^2 residues revealed that electronic effects play only a minor role. Substrates equipped with a π-donor substituent such as *p*-OMe or *p*-OH (entries 3, 4, and 9), a π-acceptor substituent such as *p*-NO_2 (entry 12), or σ-acceptor substituent such as *o*- or *p*-Cl (entries 10 and 11) as well as substrates with electron-rich heterocycles such as 2-furyl (entry 13) gave similar results in terms of yield and enantioselectivity.[25]

Table 3. Domino Azlactone Formation−Michael Addition[a]

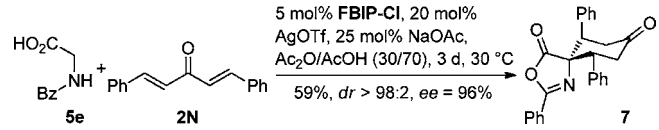


entry	3	R^1	R^2	R^3	yield (%)[b]	dr[c]	ee (%)[d]
1	**3aA**	Me	Ph	Me	95	>98:2	76
2	**3bA**	Et	Ph	Me	92	>98:2	93
3	**3bB**	Et	3,4-$(MeO)_2C_6H_3$	Me	81	>98:2	91
4	**3bC**	Et	4-HOC_6H_4[e]	Me	43	>98:2	88
5	**3bD**	Et	4−BrC_6H_4	Me	88	>98:2	92
6	**3bE**	Et	Me	Et	92	>98:2	87
7	**3bF**	Et	*n*-Pr	Me	90	>98:2	90
8	**3cA**	*n*-Pr	Ph	Me	89 (90)[f]	>98:2	98 (97)[f]
9	**3cG**	*n*-Pr	4-$MeOC_6H_4$	Me	81	>98:2	96
10	**3cH**	*n*-Pr	4-ClC_6H_4	Me	85	>98:2	98
11	**3cI**	*n*-Pr	2-ClC_6H_4	Me	82	>98:2	99
12	**3cJ**	*n*-Pr	4-$O_2NC_6H_4$	Me	76	>98:2	98
13	**3cK**	*n*-Pr	2-furyl	Me	88	>98:2	96
14[g]	**3cL**	*n*-Pr	Ph	Ph	87	98:2	90
15	**3cM**	*n*-Pr	*i*-Pr	Me	64	>98:2	>97
16[g]	**3dA**	Bn	Ph	Me	41	>98:2	81

[a] Reactions were performed with 0.27 mmol of **5** using 2.0 equiv of **2**. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC. [e] The OH group was acylated during the reaction. [f] Data in parentheses were obtained in a run using 5.0 mmol of **5c** and 1 mol % **FBIP-Cl** at 40 °C for 20 h. [g] Using 5 mol % **FBIP-Cl**, 20 mol % AgOTf, and 25 mol % NaOAc.

Dienones can be used for a double Michael addition, as exemplified for dibenzylidene acetone (**2N**, Scheme 2). Reaction with *N*-benzoylglycine (**5e**) provided the spirocyclic product **7** with excellent diastereo- and enantioselectivity.

Scheme 2. Double Michael Addition To Form Spirocyclic Product **7**



Initially, we speculated that the soft bimetallic catalyst would allow for a transition state **8** in which the azlactone would be activated by enolization promoted by coordination of the N atom. On the other side, the enone would be activated as an electrophile by face-selective coordination of the olefinic double bond to the carbophilic Lewis acid (Figure 1), similar to our previous investigations with vinyl ketones and α-cyanoacetates.[22] However, two facts seem to indicate that this mode of operation is not valid in the present case: (1) useful yields and high enantioselectivities were achieved only in the presence of acetic acid as the solvent, suggesting that one component might be activated by the Brønsted acid rather than by a Pd^{II} center; (2) the expected face selectivity[26] for the coordination of *E*-configured olefins is not in agreement with the absolute configuration of the products.[27]

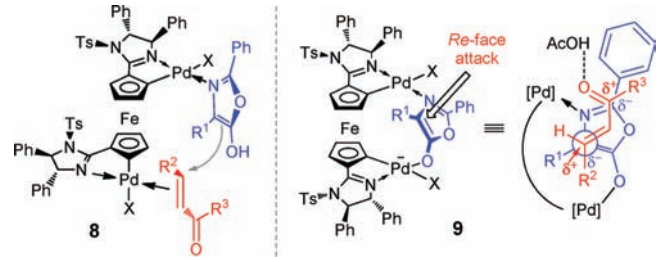
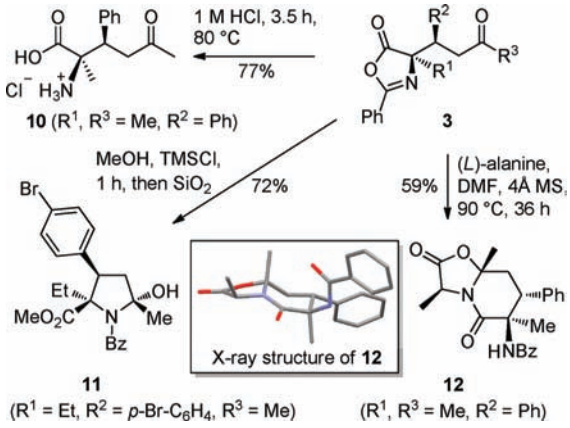


Figure 1. (left) Initially assumed activation mechanism and (right) modified working model with a bidentate azlactone coordination mode.

Our modified working hypothesis involves coordination of the bidentate azlactone to both Pd centers, which strongly activates the azlactone for enolization.[28] NaOAc likely acts as a base to deprotonate the α-position, forming enolate **9**,[29] in which the *Si* face is blocked by the ferrocene core while the *Re* face is accessible for attack by the enone, which is activated by acetic acid (Figure 1). The diastereoselectivity can be explained by assuming that the transition state adopts a staggered conformation about the developing C−C bond in which the energy is minimized by π interaction of the electron-poor enone and the electron-rich enolate possessing nucleophilic positions at C4 and C2[25] (Figure 1; see the Supporting Information for the molecular orbitals involved). A bimetallic activation mode was further confirmed by control experiments with ferrocene monopalladacycles,[30] which resulted in very low yields for the conjugate addition product (≤14%; see the Supporting Information).

The synthetic utility of the reaction products was demonstrated by nucleophilic ring opening of the conjugate addition products **3** (Scheme 3). Treatment with 1 M HCl for 3.5 h at 80 °C provided α,α-disubstituted α-amino acid **10** as the hydrochloride salt in good yield and almost diastereomerically pure form. Quaternary α-amino acids have received considerable interest[31] because they lead to unique folding when incorporated into

Scheme 3. Formation of Quaternary Amino Acid Derivatives



peptides as well as increased hydrophobicity and stability against peptide degradation.[31,32] Treatment of **3** with MeOH/TMSCl[12] furnished proline derivative **11** as a single diastereomer with one tertiary and two quaternary stereocenters. Unprotected L-alanine gave direct access to bicyclic dipeptide **12**, which also contains two quaternary centers (56% yield over two steps from racemic *N*-benzoylalanine)[33,34] and was used to determine the absolute configuration of the conjugate addition product **3aA** by X-ray crystal structure analysis (Scheme 3).[35]

In conclusion, we have reported the first catalytic asymmetric conjugate addition of azlactones to enones. This task was accomplished by cooperative activation using a soft bimetallic catalyst, a Brønsted acid, and a Brønsted base. Because of the robustness of the **FBIP** catalyst toward acetic anhydride as a cosolvent in acetic acid, a tandem azlactone formation−Michael addition was developed to generate in a single step diastereomerically pure and highly enantioenriched masked amino acids with adjacent quaternary and tertiary stereocenters starting from commercial racemic *N*-benzoyl amino acids.

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Supporting Information Available: General experimental information, NMR spectra, HPLC data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, *3*, 369.

(2) Selected examples: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204. (b) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313. (c) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (d) Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4966. (e) Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2010**, *2*, 192.

(3) Selected recent reviews about asymmetric conjugate additions: (a) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (b) Alexakis, A.; Bäckvall, J.-E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (d) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058. (e) Jautze, S.; Peters, R. *Synthesis* **2010**, 365.

(4) Reviews about catalytic asymmetric tandem reactions: (a) Enders, D.; Grondal, C.; Huettl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143.

(5) Reviews: (a) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755. (b) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432.

(6) [4 + 2] cycloaddition: Jiang, J.; Qing, J.; Gong, L.-Z. *Chem.—Eur. J.* **2009**, *15*, 7031.

(7) Steglich reaction: (a) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532. (b) Shaw, S. A.; Alemán, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368. (c) Shaw, S. A.; Alemán, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925. (d) Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914.

(8) Allylic alkylations: (a) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (b) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (c) Trost, B. M.; Jäkel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438. (d) Uraguchi, D.; Asai, Y.; Ooi, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 733.

(9) Nucleophilic ring opening: (a) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539. (b) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154. (c) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807. (d) Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892.

(10) Mannich-type reactions: (a) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088. (b) Liu, X.; Deng, L.; Jiang, X. W.; Yan, W.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 876.

(11) Aldol-type additions: (a) Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430. (b) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286.

(12) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031.

(13) Hayashi, Y.; Obi, K.; Ohta, Y.; Okamura, D.; Ishikawa, H. *Chem.—Asian J.* **2009**, *4*, 246.

(14) Nitroolefins: Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem.—Eur. J.* **2008**, *14*, 10958.

(15) Bis(phenylsulfonyl)ethylene: Alba, A.-N. R.; Companyó, X.; Valero, G.; Moyano, A.; Rios, R. *Chem.—Eur. J.* **2010**, *16*, 5354.

(16) Acyl phosphonates: Jiang, H.; Paixão, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 2775.

(17) Acyl benzotriazoles: Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120.

(18) Maleimides: Alba, A.-N. R.; Valero, G.; Calbet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Chem.—Eur. J.* [Online early access]. DOI: 10.1002/chem.201000239. Published Online: June 28, 2010.

(19) (a) Jautze, S.; Seiler, P.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1260. (b) Jautze, S.; Seiler, P.; Peters, R. *Chem.—Eur. J.* **2008**, *14*, 1430. (c) Jautze, S.; Diethelm, S.; Frey, W.; Peters, R. *Organometallics* **2009**, *28*, 2001.

(20) Recent reviews about palladacycles: (a) Djukic, J.-P.; Hijazi, A.; Flack, H. D.; Bernardinelli, G. *Chem. Soc. Rev.* **2008**, *37*, 406. (b) Dupont, J.; Pfeffer, M. *Palladacycles*; Wiley-VCH: Weinheim, Germany, 2008. (c) Richards, C. J. In *Chiral Ferrocenes in Asymmetric Catalysis*; Dai, L.-X., Hou, X.-L., Eds.; Wiley-VCH, Weinheim, Germany, 2010; pp 337−368.

(21) First preparation of chiral ferrocenyl imidazolines: Peters, R.; Fischer, D. F. *Org. Lett.* **2005**, *7*, 4137.

(22) Jautze, S.; Peters, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 9284.

(23) Selected reviews about bimetallic catalysis: (a) van den Beuken, E. K.; Feringa, B. L. *Tetrahedron* **1998**, *54*, 12985. (b) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117.

(24) Selected recent applications of imidazolines as chiral ligands in asymmetric catalysis: (a) Enthaler, S.; Hagemann, B.; Bhor, S.; Anilkumar, G.; Tse, M. K.; Bitterlich, B.; Junge, K.; Erre, G.; Beller, M. *Adv. Synth. Catal.* **2007**, *349*, 853. (b) Nakamura, S.; Hyodo, K.; Nakamura, Y.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1443. (c) Arai, T.; Yokoyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4889. (d) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Lee, H.; Li, Z.; Liang, M.; Reeves, D.; Saha, A.; Varsolona, R.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 341. (e) Review: Liu, H.; Du, D.-M. *Adv. Synth. Catal.* **2009**, *351*, 489.

(25) Although C2 versus C4 regioselectivity can be an issue for the reaction of azlactones with electrophiles,[16,17] C2 alkylation was not detected in any case in the present studies.

(26) Fischer, D. F.; Barakat, A.; Xin, Z.-q.; Weiss, M. E.; Peters, R. *Chem.—Eur. J.* **2009**, *15*, 8722.

(27) Moreover, cyclic *Z*-configured enones such as cyclohexenone gave no conjugate addition product at all, although activation of *Z*-configured olefins with **FBIP** was previously found to be more efficient than for the *E*-configured isomers.[19b] Similarly, *Z*-configured olefins were also found to be the only reactive isomers with a Pt catalyst containing the same ferrocene bisimidazoline backbone. See: Huang, H.; Peters, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 604.

(28) The O-acylated azlactones were present only in minute quantities, as determined by GC−MS and NMR analyses.

(29) Acetate also binds to the activated catalyst (X = OAc in Figure 1), as determined by ^{1}H NMR analysis.

(30) Ferrocenyl monoimidazoline palladacycles: see ref 26 and: (a) Peters, R.; Xin, Z.-q.; Fischer, D. F.; Schweizer, W. B. *Organometallics* **2006**, *25*, 2917. (b) Weiss, M. E.; Fischer, D. F.; Xin, Z.-q.; Jautze, S.; Schweizer, W. B.; Peters, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 5694. (c) Fischer, D. F.; Xin, Z.-q.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 7704. (d) Xin, Z.-q.; Fischer, D. F.; Peters, R. *Synlett* **2008**, 1495. (e) Peters, R.; Xin, Z.-q.; Maier, F. *Chem.—Asian J.* **2010**, *5*, 1770.

(31) (a) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569.
(32) (a) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349. (b) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (c) Khosla, M. C.; Stachowiak, K.; Smeby, R. R.; Bumpus, F. M.; Piriou, F.; Lintner, K.; Fermandjian, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 757.
(33) For nucleophilic ring opening with O-protected amino acids and further derivatization of azlactones, see refs 5, 8d, and 12.
(34) The synthesis of a structurally related bicyclic compound lacking quaternary stereocenters (six steps, yield 2.7%) for the preparation of conformationally constrained Val−Phe dipeptidomimetics was recently reported. See: Gilleron, P.; Millet, R.; Domarkas, J.; Farce, A.; Houssin, R.; Hénichart, J.-P. *J. Pept. Sci.* **2006**, *12*, 140.
(35) Supplementary crystallographic data for **12** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) under deposition number CCDC 780031. These data are available from the CCDC at http://www.ccdc.cam.ac.uk/products/csd/request/.

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