Asymmetric Catalysis

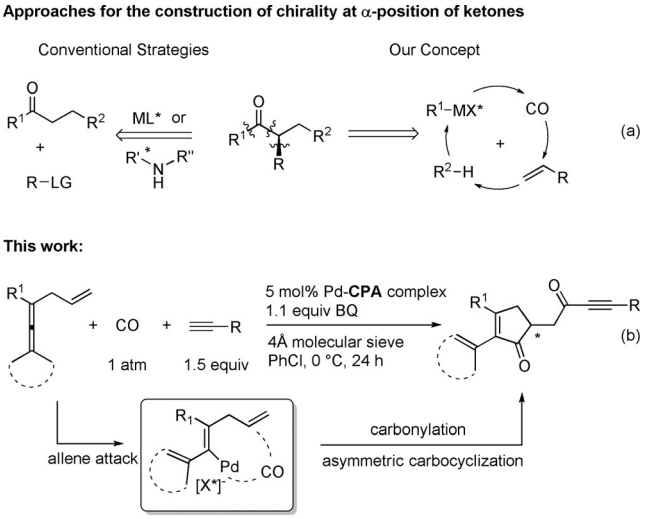
International Edition: DOI: 10.1002/anie.201612385
German Edition: DOI: 10.1002/ange.201612385

Enantioselective Palladium-Catalyzed Carbonylative Carbocyclization of Enallenes via Cross-Dehydrogenative Coupling with Terminal Alkynes: Efficient Construction of α-Chirality of Ketones

Bin Yang, Youai Qiu, Tuo Jiang, William D. Wulff, Xiaopeng Yin, Can Zhu, and Jan-E. Bäckvall**

Abstract: *An enantioselective Pd^{II}/Brønsted acid-catalyzed carbonylative carbocyclization of enallenes ending with a cross-dehydrogenative coupling (CDC) with a terminal alkyne was developed. VAPOL phosphoric acid was found as the best co-catalyst among the examined 28 chiral acids, for inducing the enantioselectivity of α-chiral ketones. As a result, a number of chiral cyclopentenones were easily synthesized in good to excellent enantiomeric ratio with good yields.*

Transition metal-catalyzed enantioselective transformation/functionalization of carbonyl compounds is an indispensable tool to install molecular chirality. The pioneering work[1] by Buchwald, Hartwig, and Miura suggested that Pd^0-catalyzed direct asymmetric α-arylation of carbonyl compounds with aryl halides is a viable approach to introduce chirality at the α-position of carbonyl group. Based on this approach, conventional protocols on asymmetric cross-coupling reactions of different types of carbonyl group have been well established with a chiral ligand or chiral amine (Scheme 1a, left).[2] Moreover, methodologies using stoichiometric amounts of chiral auxiliaries were also reported for the construction of chirality at the α-position of ketones.[3] On the other hand, cascade carbon–carbon (C–C) bond formation involved in carbocyclizations is highly attractive, due to its atom economy and step efficiency. Previous work within our research group has shown that enantioselective oxidative carbocyclization of unsaturated structures can be achieved by exchanging the anion of a Pd^{II} salt into chiral one.[4] On the basis of this concept, the strategy using a cascade insertion of carbon monoxide (CO) and an olefin would give cyclic carbonyl compounds with high efficiency (Scheme 1a, right). Therefore, the use of a suitable chiral counterion $[X^*]^-$ could, in principle, give chiral carbonyl products, for example, ketones. However, previous examples of CO insertion for construction of chirality at the α-position of newly formed carbonyls gave low chemo-,[5a,b] regio-[5b] and enantioselectivities.[5c] Thus, we envisaged that the challenge will be the identification of suitable chiral catalyst systems, which would work nicely in each step during this insertion cascade, considering the fact that CO is a strong ligand towards a transition metal.

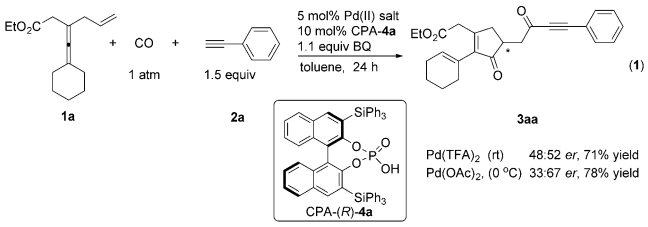


Scheme 1. Approaches to introduce chirality at α-position of carbonyl groups. L* = chiral ligand. LG = leaving group. $[X^*]^-$ = chiral anion. CPA = chiral phosphoric acid.

Our group has previously been involved in the Pd^{II}-catalyzed oxidative transformation of different types of allenes[6] under oxidative conditions.[7] Recently, we reported on a palladium-catalyzed oxidative carbonylation–carbocyclization–carbonylation–alkynylation of enallenes with four C–C bond formations.[8a] This cascade reaction proceeded via efficient and selective insertion of CO, olefin, and CO. We anticipated that, in the presence of a suitable chiral source, it would be possible to develop an asymmetric version of this cascade reaction. However, the choice of source of chirality for CDC is rather limited. One reason is that the commonly used ligands (e.g. phosphine ligands) are quite sensitive under such oxidative conditions. The second reason is that, in this system, the olefin unit needs to coordinate to Pd^{II} to trigger the allene attack,[8b] and the addition of a polydentate ligand would prevent this coordination.[9] Herein, we report our recent development on the efficient Pd^{II}/chiral phosphoric acid (CPA)-catalyzed asymmetric carbonylative carbocyclization of enallenes (Scheme 1b).

[*] B. Yang, Dr. Y. Qiu, Dr. T. Jiang, Dr. C. Zhu, Prof. Dr. J.-E. Bäckvall
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University
SE-106 91, Stockholm (Sweden)
E-mail: zhucaner@gmail.com
jeb@organ.su.se
Prof. Dr. W. D. Wulff, X. Yin
Department of Chemistry, Michigan State University
MI 48824, East Lansing (USA)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201612385.

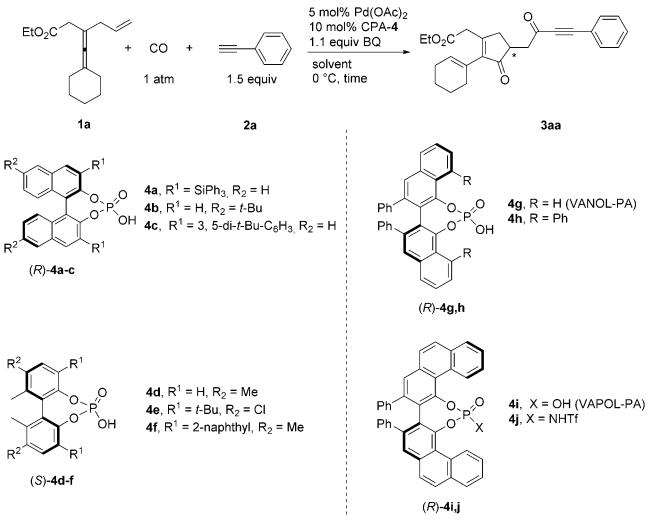
Based on the previous optimal reaction conditions,[8a] the initial asymmetric coupling reaction was carried out by treating allyl-substituted 3,4-dienoate **1a** with alkyne **2a** (1.5 equiv), BQ (1.1 equiv), $Pd(TFA)_2$ (TFA = trifluoroacetate) (5 mol%), and chiral phosphoric acid (*R*)-**4a** (10 mol%) in toluene at room temperature (rt) under 1 atm of CO (balloon). The desired carbocycle **3aa** was formed in 71% yield (determined by ^{1}H NMR analysis), and its enantiomeric ratio (*er*) was 48:52 [Eq. (1)]. By changing the Pd source to



$Pd(OAc)_2$ and running the reaction at 0 °C, a better enantiomeric ratio (*er*, 33:67) of the product was achieved with 78% yield. It is worth noting that this transformation catalyzed by $Pd(OAc)_2$ without chiral phosphoric acid gave **3aa** in only 43% yield, indicating that the pK_b value of the corresponding anion (phosphate vs. acetate) will affect the reactivity dramatically. With these results in hand, we set out to screen a series of chiral acids. Chiral phosphoric acids with BINOL scaffold, which was the superior co-catalyst in a previous asymmetric carbonylation study,[10,11] showed poor enantioselectivity in the transformation of **1a** to **3aa** (Table 1, entry 2). Among the chiral acids tested, (*R*)-3,3′-bis-(3,5-di(*tert*-butyl)phenyl)-substituted BINOL phosphoric acid **4c** gave the best *er* (28.5:71.5) with 63% yield (Table 1, entry 3). We further examined phosphoric acids with a biphenol scaffold, which had shown excellent enantioselectivity in previous carbocyclization studies (Table 1, entries 4–6).[5b] However, no significant improvement in the enantioselectivity was observed. Phosphoric acid **4f** was found to be the most efficient co-catalyst among its analogues tested, giving **3aa** in 76% yield with 71:29 *er* (Table 1, entry 6). CPAs with other scaffolds were also screened. (For details, see SI). Moreover, chiral acid **4g** [(*R*)-VANOL phosphoric acid][12] was found to provide a 78:22 *er* under the same reaction conditions (Table 1, entry 7). Phenyl substitution on VANOL phosphoric acid (R = Ph, **4h**) on the other hand lowered the enantioselectivity (e.r. = 54:46) and gave a low reaction rate (Table 1, entry 8). To our delight, one more fused benzene ring (VAPOL phosphoric acid **4i**) increased the enantiomeric ratio further to 88:12 with 73% yield (Table 1, entry 9). VAPOL phosphoramide **4j** was also tested: the reaction gave 81% yield, but the enantioselectivity dropped dramatically (*er* 56:44) (Table 1, entry 10).

Intrigued by the results of the chiral acid screening, we next set out to optimize the reaction conditions using VAPOL phosphoric acid **4i**. To our surprise, the reaction in dry toluene provided a slight improvement on both yield and enantioselectivity of the product (Table 1, entry 15). Furthermore, anhydrous chlorobenzene was found to be the best

Table 1: Selective results for the screening of chiral acids.[a]



Entry	Chiral acid	Reaction time	Solvent	Yield of **3aa** [%][b]	*er* of **3aa**[c]
1	(*R*)-**4a**	24 h	toluene	78	33:67
2	(*R*)-**4b**	24 h	toluene	65	44.5:55.5
3	(*R*)-**4c**	24 h	toluene	63	28.5:71.5
4	(*S*)-**4d**	40 h	toluene	69	43.5:56.5
5	(*S*)-**4e**	24 h	toluene	67	41.5:58.5
6	(*S*)-**4f**	24 h	toluene	76	71:29
7	(*R*)-**4g**	24 h	toluene	68	78:22
8	(*R*)-**4h**	24 h	toluene	22[d]	54:46
9	(*R*)-**4i**	22 h	toluene	73	88:12
10	(*R*)-**4j**	24 h	toluene	81	56:44
11[e,f]	(*R*)-**4i**	24 h	*p*-xylene	73	91:9
12	(*R*)-**4i**	24 h	fluorobenzene	67	87:13
13	(*R*)-**4i**	24 h	DCM	37	80:20
14	(*R*)-**4i**	24 h	THF	40[d]	81:19
15[f]	(*R*)-**4i**	24 h	toluene	84	91.5: 8.5
16[f]	(*R*)-**4i**	24 h	chlorobenzene	83	92.5:7.5
17	(*R*)-**4i**	24 h	chlorobenzene	70	87:13
18[g]	(*R*)-**4i**	24 h	chlorobenzene	68	85.5:14.5
19[f,h,i]	(*R*)-**4i**	24 h	chlorobenzene	82[j]	95:5

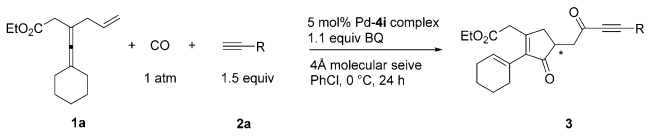
[a] $Pd(OAc)_2$ was stirred together with chiral acid in the indicated solvent at 50 °C for 5 min, then the other starting materials were added and the reaction was run on 0.1 mmol scale in 1 mL under 1 atm CO. [b] Yields were determined by ^{1}H NMR analysis of crude reaction mixture using anisole as the internal standard. [c] Determined by chiral HPLC. [d] Starting material was not fully consumed. [e] Room temperature was used instead. [f] Anhydrous solvent was used. [g] 20 mol% of AcOH was added. [h] The pre-made Pd^{II}-VAPOL phosphate complex[12] was used instead. [i] 6 mg mL^{-1} of 4 Å M.S. was added. [j] Isolated yield. PA = phosphoric acid.

solvent, which afforded 83% yield of **3aa** (Table 1, entry 16) with a 92.5:7.5 *er*. Solvents, which were not dried, gave a lower enantioselectivity than anhydrous solvents (Table 1, entry 9 vs. 15 and entry 16 vs. 17). In addition, using acetic acid as additive was found to decrease both *er* and yield of **3aa** (Table 1, entry 17 vs. 18). The reaction conditions were further investigated and it was found that reaction with a higher catalyst loading does not give any improvement of neither yield nor enantioselectivity. However, the addition of molecular sieves (M.S.) and using pre-made Pd^{II}-VAPOL phosphate complex[13] as the catalyst system further increased

the *er* of **3aa** to 95:5 with a maintained good yield (Table 1, entry 19).

After having the optimized reaction conditions in hand, the scope of terminal alkynes **2** was investigated using enallene **1a** (Table 2). First, a number of functionalized

Table 2: Scope of terminal alkynes.

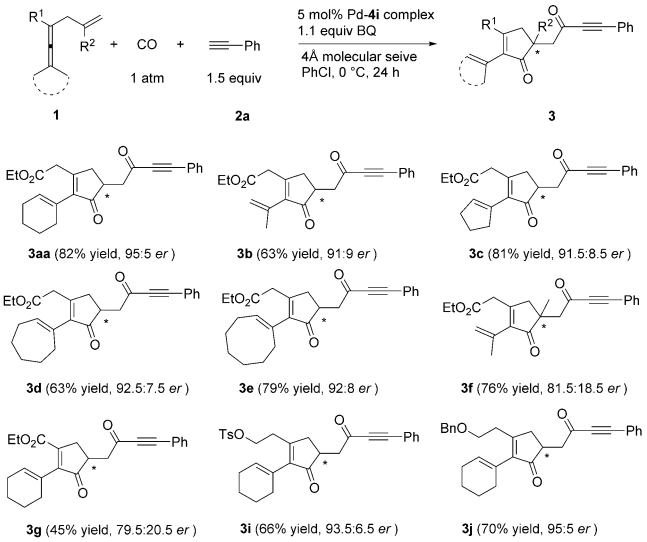


Entry	R	Product	Yield of **3** [%][b]	*er* of **3**[c]
1	Ph (**2a**)	**3aa**	82	95:5
2	4-$MeOC_6H_4$ (**2b**)	**3ab**	76	95:5
3	2-$MeOC_6H_4$ (**2c**)	**3ac**	81	92.5:7.5
4	4-FC_6H_4 (**2d**)	**3ad**	48	91.5:8.5
5	4-ClC_6H_4 (**2e**)	**3ae**	75	93.5:6.5
6	4-BrC_6H_4 (**2f**)	**3af**	71	95.5:4.5
7	4-MeC_6H_4 (**2g**)	**3ag**	74	95:5
8	4-$CF_3C_6H_4$ (**2h**)	**3ah**	79	95:5
9	3-chloropropyl (**2i**)	**3ai**	66	92:8
10	2-thiophenyl (**2j**)	**3aj**	64	92:8
11	3-thiophenyl (**2k**)	**3ak**	69	93.5:6.5
12	cinnamyl (**2l**)	**3al**	73	93.5:6.5
13	TMS (**2m**)	**3am**	5[d]	56.5:43.5

[a] Reactions were run on 0.1 mmol scale in 1.0 mL of chlorobenzene. [b] Yield of isolated product after column chromatography. [c] Determined by chiral HPLC. [d] The reaction was run for 60 h, and the yield was determined by ^{1}H NMR analysis of the crude reaction mixture using anisole as the internal standard.

phenylacetylenes were examined: the analogues substituted with *p*-MeO, *o*-MeO, *p*-Me, *p*-F, *p*-Cl, *p*-Br and *p*-CF_3 groups all reacted nicely and afforded the corresponding products **3ab–ah** in good yields with good to high *er* (up to 95.5:4.5) (Table 2, entries 2–8). The asymmetric reaction tolerates heteroaryl acetylenes, as well as aliphatic acetylenes (Table 2, entries 9–12). Alkyne with a substituent of TMS (TMS = trimethylsilyl) gave **3am** in only 5% yield and very low *er* (56.5:43.5) with a reaction time of 60 h (Table 2, entry 13). It is obvious that the reaction rate with alkyne **2m** is much lower compared to that of phenylacetylene (**2a**), and the *er* of the product from acetylene **2m** was poor. Thus, slow alkyne-quenching of the key palladium species appears to lead to poor enantioselectivity of the corresponding product, implying possible racemization of the chiral intermediate during the reaction.

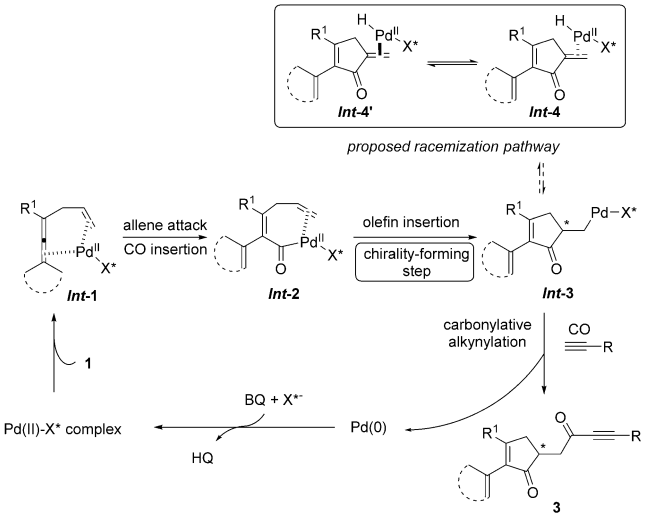
With these results in hand, we continued to investigate the scope of enallenes in this reaction (Scheme 2). By changing the terminal cycloalkyl group at the allene moiety to two methyl groups, a slight decrease of enantiomeric ratio of **3b** was observed. The ring size was further studied and we found all derivatives reacted smoothly although the *er* values of the corresponding products (**3c–e**) were slightly lower than those of the six-membered rings. Adding internal methyl substitution to the olefin moiety resulted in a lower *er* of the product **3f**. Substituents on the allene moiety were also studied, and



Scheme 2. Scope of enallenes.

found to have significant influences on both enantioselectivity and reactivity. Using 2,3-allenoate (**1g**) instead of 3,4-allenoate as the starting material led to a much lower *er* (79.5:20.5) and yield (45%). Other functional groups such as sulfonyl ester and ether were found to be compatible with the the reaction conditions, thus giving good enantioselectivities and yields (**3i** and **3j**).

A proposed mechanism for this asymmetric cascade reaction is shown in Scheme 3. The insertion cascade starts with the coordination of enallene to Pd^{II} giving intermediate ***Int*-1**. The subsequent allene attack and CO insertion on chiral Pd^{II} species forms carbonyl Pd^{II} intermediates ***Int*-2**.[8] Enantioselective migratory insertion of the olefin into the C-Pd bond would produce the carbocyclic intermediate ***Int*-3**, introducing the chirality at the α-position of the ketone. Finally, carbonylative alkynylation of ***Int*-3** would give product **3**, and the released Pd^0 would be subsequently



Scheme 3. Proposed mechanism for the introduction of chirality onto α-position of ketones via cascade CO–olefin–CO insertion.

reoxidized to Pd^{II} by BQ to close the catalytic cycle. By isolating the unexpected olefin byproduct from β-elimination of ***Int*-3** in a control experiment,[14] we propose a racemization pathway which might lower the *er* of **3**. When the carbonylative alkynylation step is slow (e.g. R = TMS), ***Int*-3** could go to ***Int*-4** via β-hydride elimination. Isomerization of ***Int*-4** would result in ***Int*-4′** leading racemization of the formed chirality. To determine the absolute configuration of product **3aa**, diastereoselective 1,2-reduction of the 2-substituted 4-cyclopenten-1-one group followed by MTPA ester analysis was carried out. The results suggest that (*S*)-**3aa** is the predominant enantiomer from the reaction with the (*R*)-VAPOL phosphate ligand.[15]

In conclusion, we have developed a Pd^{II}/VAPOL phosphoric acid-catalyzed asymmetric dehydrogenative carbonylation-carbocyclization reaction of enallenes for the construction of α-chirality of ketones. This asymmetric process is highly efficient, and proceeds via cascade CO insertion and enantioselective olefin insertion. Vaulted biaryl-type chiral phosphoric acids served as useful co-catalysts for this asymmetric transformation. With this method, a number of enantiomerically enriched carbocycles were obtained in good yields with good to high enantioselectivity. More importantly, this work provides a new strategy to introduce chirality at the α-position of carbonyl compounds. Further studies on the mechanism and application of this method are currently under way in our laboratory.

Acknowledgements

Financial support from the European Research Council (ERC AdG 247014), The Swedish Research Council (621-2013-4653), The Berzelii Center EXSELENT, and the Knut and Alice Wallenberg Foundation is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric carbocyclization · enallenes · homogeneous catalysis · oxidation · palladium

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 4535–4539
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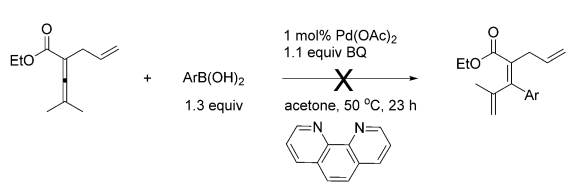

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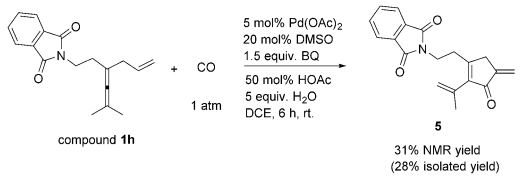
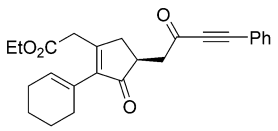
[12] For the synthesis of vaulted biaryl diol-based phosphoric acid, see: a) J. Bao, W. D. Wulff, J. B. Dominy, M. J. Fumo, E. B. Grant, A. C. Rob, M. C. Whitcomb, S.-M. Yeung, R. L. Ostrander, A. L. Rheingold, *J. Am. Chem. Soc.* **1996**, *118*, 3392; b) Z. Ding, W. E. G. Osminski, H. Ren, W. D. Wulff, *Org. Process Res. Dev.* **2011**, *15*, 1089; c) A. A. Desai, W. D. Wulff, *Synthesis* **2010**, 3670; d) A. A. Desai, L. Huang, W. D. Wulff, G. B. Rowland, J. C. Antilla, *Synthesis* **2010**, 2106. For examples of applications of vaulted biaryl diol-based phosphoric acids, see: e) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696; f) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830; g) E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 12084; h) W. Zheng, Z. Zhang, M. J. Kaplan, J. C. Antilla, *J. Am. Chem. Soc.* **2011**, *133*, 3339; i) S. E. Larson, G. Li, G. B. Rowland, D. Junge, R. Huang, H. L. Woodcick, J. C. Antilla, *Org. Lett.* **2011**, *13*, 2188.

[13] 1 equiv of $Pd(OAc)_2$ and 2 equiv of VAPOL phosphoric acid was stirred in dry CH_3Cl overnight, the reaction mixture turned into red. The solvent was removed and the residue was heated at 50 °C under vacuum for two days to remove generated AcOH. Pd^{II}-VAPOL phosphate complex was obtained as a dark red powder.

[14] The proposed β-hydride elimination product was isolated under slightly modified reaction conditions.



[15] See the Supporting Information for a detailed discussion on determination of the absolute configuration of **3aa** generated from (*R*)-VAPOL phosphate ligand.



(*S*)-**3aa**

Manuscript received: December 21, 2016
Final Article published: March 27, 2017

