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Dual Amine and Palladium Catalysis in Diastereo- and Enantioselective Allene Carbocyclization Reactions

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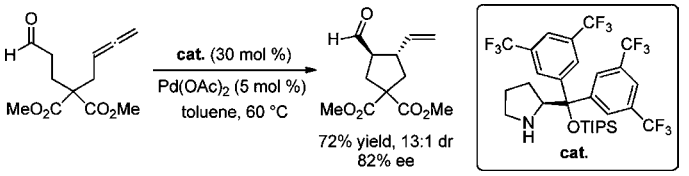
ABSTRACT



A pyrrolidine and Pd catalyzed diastereoselective carbocyclization of aldehyde and ketone-linked allenes has been developed. The cooperative organo/metal-catalyzed cyclization reaction, which presumably proceeds via an enamine intermediate, is efficient and broad in scope. Also, it has been extended to a catalytic asymmetric variant using diarylprolinol-based organocatalysts to afford substituted cyclopentane and pyrrolidine reaction products in up to 82% ee.

Combining two or more catalytically active species in one reaction vessel can unlock new reaction pathways for substrates and reagents not accessible by the individual catalysts operating alone. Working either as mutually compatible catalyst systems in separate catalytic cycles or in cooperative harmony during bond formation, this field of dual catalysis is emerging as a powerful tool in organic synthesis and is mostly evident when enamine or iminium ion catalysis meets transition metal (ion) catalysis.[1,2] Pioneering work by Córdova demonstrated that α-allylation of aldehydes with allyl acetates was possible using a combination of amine and Pd catalysts.[3] Later, Saicic reported a new method for the construction of five- or six-membered rings via organocatalyzed cyclization of π-allylpalladium complexes.[4] Similary, Kirsch et al. were able to combine gold and amino catalysis in a carbocyclization of alkyne-linked aldehydes.[5] At the same time, our group developed a one-pot, pyrrolidine- and Cu(I)-catalyzed multistep reaction cascade sequence of α,β-unsaturated ketones and propargylated malonates to form cyclopentene products.[6] The catalyzed cascade, which we postulated to proceed via iminium, enamine, and metal (ion) activation modes, was also successful with pyrrolidine and Ag(I), Au(I), Hg(II), or Pd(0) catalyst combinations. In a continuation of this research program, we wanted to extend our work on amine and transition metal catalyzed carbocyclizations of alkynes to include allene-linked ketones and aldehydes. Cyclization reactions involving carbopalladation have emerged as a powerful strategy to construct complex carbocycles.[7] Among the many C−C bond formations that proceed through a Pd-catalyzed activation of allenes toward nucleophilic attack, the addition

(1) (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745–2755. (b) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999–3025. (c) Stegbauer, L.; Sladojevich, F.; Dixon, D. J. *Chem. Sci.* **2012**, *3*, 942–958.

(2) (a) Lin, S.; Zhao, G.-L.; Deiana, L.; Sun, J.; Zhang, Q.; Leijonmarck, H.; Córdova, A. *Chem.—Eur. J.* **2010**, *16*, 13930–13934. (b) Zweifel, T.; Hollmann, D.; Prüger, B.; Nielsen, M.; Jørgensen, K. A. *Tetrahedron: Asymmetry* **2010**, *21*, 1624–1629. (c) Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 1750–1753. (d) Patil, N. T.; Raut, V. S. *J. Org. Chem.* **2010**, *75*, 6961–6964. (e) Afewerki, S.; Breistein, P.; Pirttilä, K.; Deiana, L.; Dziedzic, P.; Ibrahem, I.; Córdova, A. *Chem.—Eur. J.* **2011**, *17*, 8784–8788.

(3) (a) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952–1956. (b) Afewerki, S.; Ibrahem, I.; Rydfjord, J.; Breistein, P.; Córdova, A. *Chem.—Eur. J.* **2012**, *18*, 2972–2977.

(4) Bihelovic, F.; Matovic, R.; Vulovic, B.; Saicic, R. N. *Org. Lett.* **2007**, *9*, 5063–5066.

(5) Binder, J.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025–1028.

(6) Yang, T.; Ferrali, A.; Campbell, L.; Dixon, D. J. *Chem. Commun.* **2008**, 2923–2925.

(7) (a) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12–21. (b) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516. (c) Negishi, E.; Wang, G.; Zhu, G. *Top Organomet. chem* **2006**, *19*, 1–48.

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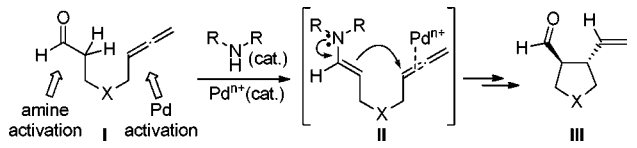
of activated methylene compounds[8–10] has been well-studied.

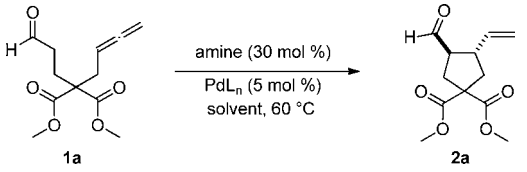
Scheme 1. Concept of an Amine and Pd Catalyzed Cycloisomerization of Aldehyde-Linked Allenes



Accordingly, through an appropriate combination of amine and transition metal catalysts, in particular Pd catalysts, we believed substrates of type **I** could be transformed into cyclic products of type **III** via enamine and Pd activated intermediates such as **II** (Scheme 1). Furthermore, through judicious choice of the catalysts employed, achieving good diastereo- and enantioselectivity was a real possibility. Herein we report our findings.

Initial proof of reactivity studies were performed on allene-linked aldehyde **1a** using 5 mol % of $Pd(PPh_3)_4$. Pleasingly on the first attempt, treatment of **1a** with both 5 mol % $Pd(PPh_3)_4$ and 30 mol % pyrrolidine in $CHCl_3$ at 60 °C resulted in the formation of the desired cyclic product **2a** in 45% yield with 11:1 dr (Table 1, entry 1). Two control experiments were performed which demonstrated that, in the absence of either the pyrrolidine or Pd catalyst, no reaction took place (Table 1, entries 2 and 3). These results strongly support the dual activation mechanism proposal for achieving reactivity. Various amines were then investigated. Changing pyrrolidine to piperidine led to diminished reaction conversion and diastereoselectivity (Table 1, entries 1 and 4). Only a trace amount of product was observed when 30 mol % morpholine was used (Table 1, entry 5), presumably because of the lower nucleophilicity of the morpholine secondary amine. Good diastereoselectivity was obtained using diisopropylamine as the organocatalyst, but the reaction showed very low conversion (Table 1, entry 8). No reaction occurred using L-proline, even if the polar solvent DMSO was used to improve solubility (Table 1, entries 6 and 7). Changing the Pd catalyst from $Pd(PPh_3)_4$ to $Pd(OAc)_2$ led to an increase in reaction yield and diastereoselectivity (Table 1, entries 1 and 10). Screening some typical reaction solvents in the presence of 5 mol % $Pd(OAc)_2$ and 30 mol % pyrrolidine demonstrated that toluene provided the best results, in terms of both the yield (68%) and diastereoselectivity

Table 1. Catalyst Identification and Reaction Optimization



	amine	PdL_n	solvent	time (h)	conv (%)	yield (%)[a]	dr[b]
1	pyrrolidine	$Pd(PPh_3)_4$	$CHCl_3$	16	73	45	11:1
2	–	$Pd(PPh_3)_4$	$CHCl_3$	16	NR	–	–
3	pyrrolidine	–	$CHCl_3$	16	NR	–	–
4	piperidine	$Pd(PPh_3)_4$	$CHCl_3$	24	60	–	5:1
5	morpholine	$Pd(PPh_3)_4$	$CHCl_3$	24	trace	–	–
6	L-proline	$Pd(PPh_3)_4$	$CHCl_3$	24	NR	–	–
7	L-proline	$Pd(PPh_3)_4$	DMSO	24	NR	–	–
8	DIPA	$Pd(PPh_3)_4$	$CHCl_3$	24	22	–	10:1
9	(*R*)-PhCH(Me)NH_2	$Pd(PPh_3)_4$	$CHCl_3$	24	NR	–	–
10	pyrrolidine	$Pd(OAc)_2$	$CHCl_3$	14	100	58	13:1
11	pyrrolidine	$Pd(OAc)_2$	THF	14	100	51	13:1
12	pyrrolidine	$Pd(OAc)_2$	1,4-dioxane	14	100	46	13:1
13	pyrrolidine	$Pd(OAc)_2$	CH_3CN	14	100	32	12:1
14	**pyrrolidine**	**$Pd(OAc)_2$**	**toluene**	**14**	**100**	**68**	**13:1**
15	pyrrolidine	$Pd(OAc)_2$	DMF	14	100	42	12:1
16[c]	pyrrolidine	$Pd(OAc)_2$	toluene	20	100	39	10:1
17[d]	pyrrolidine	$Pd(OAc)_2$	toluene	13	100	46	10:1
18[e]	pyrrolidine	$Pd(OAc)_2$	toluene	16	20	–	–

[a] Isolated yields of two diastereomers. [b] Determined by analysis of the crude sample by ^1H NMR spectroscopy. [c] With 50 mol % Et_3N. [d] With 50 mol % benzoic acid. [e] With 20 mol % pyrrolidine.

(13:1 dr) (Table 1, entry 14). Lowering the pyrrolidine percentage to 20 mol % led to a significant loss in reaction efficiency, with only 20% conversion being observed using toluene as solvent at 60 °C for 16 h (Table 1, entry 18).

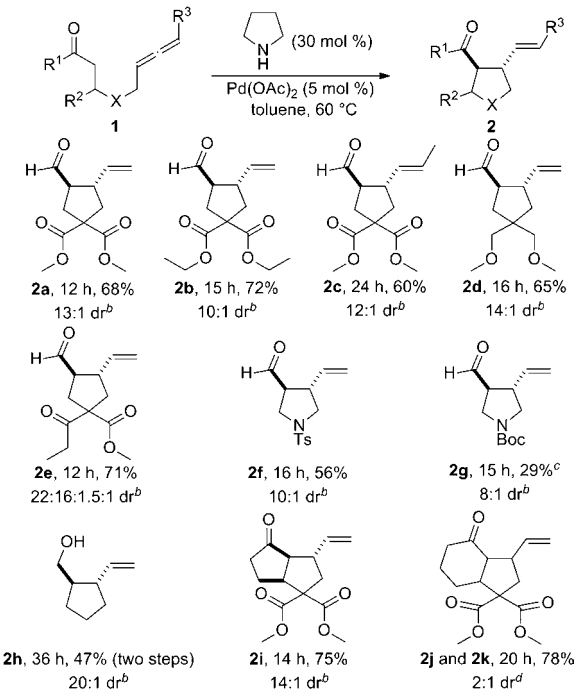
With the optimal reaction conditions identified, a range of allene-linked aldehyde and ketone substrates **1** were subjected to the carbocyclization reaction. Substrates having all-carbon chains between the carbonyl and allene units led to the desired products in good yield and diastereoselectivity (Scheme 2). Substrates with geminal substituents on the chain, such as malonates **1a** and **1b**, diether **1d**, and ketoester **1e**, all proceeded faster than those without (**1h**), presumably due to a Thorpe–Ingold effect. An aldehyde possessing an internal allene also afforded the desired product with good selectivity, but after a longer reaction time (**1c**). Substrates possessing a nitrogen atom in the chain also gave the desired products with good diastereoselectivity although in lower yields (**1f** and **1g**). Notably, subjection of cyclic ketones to the optimal conditions gave the desired cyclization products, but after a longer reaction time. In the case of the five-membered cyclic ketone **1i**, cyclization gave the product **2i** in 75% yield and 14:1 dr. The six-membered cyclic ketone **1j** afforded diastereomeric products **2j** and **2k** in 78% yield with 2:1 dr.

(8) (a) Besson, L.; Gore, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853–3856. (b) Hiroi, K.; Kato, F.; Yamagata, A. *Chem. Lett.* **1998**, 397–398. (c) Kato, F.; Hiroi, K. *Chem. Pharm. Bull.* **2004**, *52*, 95–103.

(9) (a) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156–5157. (b) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019–6020. (c) Yamamoto, Y. *Pure Appl. Chem.* **1996**, *68*, 9–14. (d) Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453–7456. (e) Trost, B. M.; Jäkel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438–4439. (f) Trost, B. M.; Simas, A. B. C.; Plietker, B.; Jäkel, C.; Xie, J. *Chem.—Eur. J.* **2005**, *11*, 7075–7082. (g) Trost, B. M.; Xie, J.; Sieber, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 20611–20622.

(10) Li, M.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 3784–3787.

Scheme 2. Reaction Scope[a]



[a] Isolated yield of diastereomers. [b] Determined by ^{1}H NMR spectroscopy after flash column chromatography. [c] **2g′** also isolated in 20% yield (see Supporting Information). [d] Separable isomers.

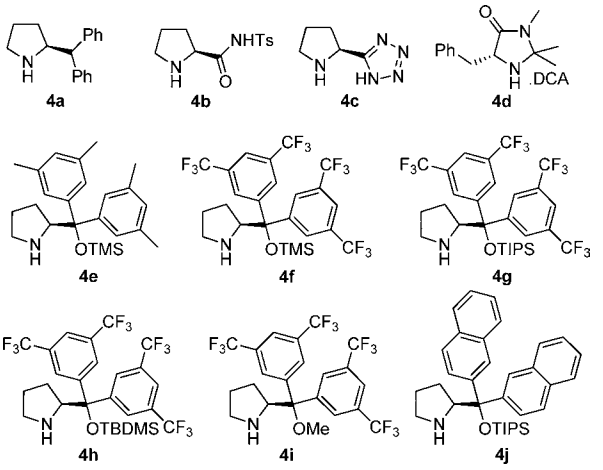
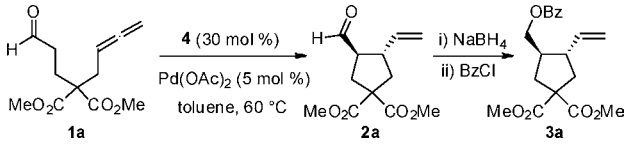


Figure 1. Organocatalysts screened in the asymmetric variant.

Table 2. Screen of Chiral Secondary Amine Organocatalysts



	4	time (h)	yield (%)[a] of 2a	dr of 2a[b]	yield (%)[a] of 3a	dr of 3a[b]	ee (%)[c] of 3a
1	**4a**	36	24	10:1	85	10:1	39
2	**4b**	36	NR	–	–	–	–
3	**4c**	36	NR	–	–	–	–
4	**4d**	48	36	13:1	87	13:1	46[d]
5	**4e**	20	59	14:1	80	14:1	60
6	**4f**	12	65	11:1	88	11:1	67
7	**4g**	20	72	13:1	89	13:1	84
8	**4h**	12	70	12:1	79	12:1	79
9	**4i**	12	62	13:1	75	13:1	79
10	**4j**	20	58	12:1	82	12:1	55

[a] Isolated yield of two diastereomers. [b] Determined by ^{1}H NMR spectroscopy after flash column chromatography. [c] Determined by chiral HPLC analysis. [d] Opposite enantiomer obtained.

We then investigated a catalytic enantioselective variant of the carbocyclization reaction by replacing pyrrolidine with various chiral cyclic secondary amine organocatalysts (Figure 1). With model substrate **1a**, no reaction occurred when proline-derived catalysts **4b** and **4c** were employed (Table 2, entries 2 and 3). Pleasingly, however, the product **2a** was obtained using MacMillan's catalyst[11] **4d** with 13:1 dr and 46% ee (Table 2, entry 4), and also using chiral pyrrolidine **4a** which afforded the product **2a** with 10:1 dr and 39% ee (Table 2, entry 1). Higher levels of asymmetric induction were achieved using the L-proline-derived Jørgensen/Hayashi type[12] catalysts **4e**–**4j** (Table 2, entries 5–10). A range of these catalysts with variations in the geminal aromatic rings as well as the O-protecting group were investigated. O-TMS protected catalyst **4f** possessing 3,5-bis(trifluoromethyl)phenyl groups out-performed catalyst **4e** possessing 3,5-dimethylphenyl groups (67 vs 60% ee, Table 2, entry 6 vs 5). With a series of catalysts possessing 3,5-bis(trifluoromethyl)-phenyl groups, the enantioselectivity improved when the steric bulk of the silyl group was increased. For example O-TIPS protected catalyst **4g** afforded the desired product with 84% ee and 13:1 dr (Table 2, entry 7), while O-TMS protected catalyst **4f** only gave a product with 67% ee (Table 2, entry 6).

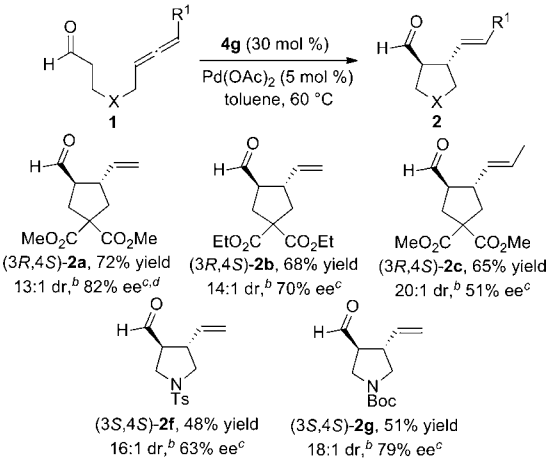
The scope of this enantioselective carbocyclization with the optimal catalyst **4g** is presented in Scheme 3. Diethyl malonate **1b** afforded the cyclopentane product **2b** in 68% yield and 70% ee. Internal allene **1c** progressed efficiently to give cyclized product **2c** with 51% ee. *N*-Tosyl allene **1f** cyclized smoothly to the desired product **2f** in 63% ee and 16:1 dr. The *N*-Boc derivative **1g** afforded cyclized product **2g** with good enantioselectivity (79% ee) and in moderate yield.

The mechanism of this new carbocyclization reaction under dual cyclic secondary amine and Pd catalysis is

(11) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585.

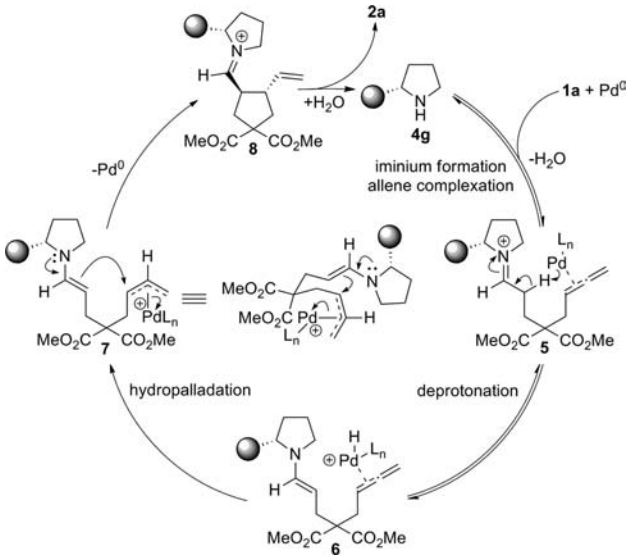
(12) (a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjrsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

Scheme 3. Scope of the Enantioselective Variant[a]



[a] Isolated yield of two diastereomers. [b] Determined by ^{1}H NMR spectroscopy after flash column chromatography. [c] Determined by chiral HPLC analysis of the purified benzoate ester derivatives. [d] The absolute stereochemistry of (3*R*,4*S*)-**2a** was determined by single crystal X-ray analysis of a derivative (see Supporting Information).

Scheme 4. Proposed Mechanism of Secondary Amine/Pd Catalyzed Carbocyclization Reaction



intriguing and worthy of further comment. From the data obtained in Table 1, it is most likely that Pd(0) (either added from the beginning or generated in situ by reduction of Pd(II) with excess secondary amine) is key to the observed reactivity. Accordingly, we propose the following mechanistic pathway which is in line with those of Trost and Yamamoto[9] in related reactions using acidic pronucleophiles. Initially, a rapid and reversible condensation of **4g** with **1a**, and a concomitant complexation of Pd(0), gives iminium ion intermediate **5** (Scheme 4). The proximally located Pd(0) species then removes the acidic α-proton[9g] of the iminium ion thus forming enamine **6** bearing the hydridopalladium(II) complexed allene. A subsequent hydropalladation of the allene moiety generates reactive π-allyl complex **7** which is then poised to undergo intramolecular nucleophilic attack by the enamine to form iminium ion **8**. Pd(0) is released back into the catalytic cycle and hydrolysis of the iminium ion yields the desired product **2a** and the regenerated catalyst **4g**.

Alternative mechanistic scenarios can be envisaged,[13] and further mechanistic studies are required, but our proposed mechanism not only follows a logical set of steps but also offers a plausible rationale for the observed stereochemical outcome.[14] Based on a reactive s-*trans* intermediate **7**, and with the assumption that C−C bond formation is enantiodetermining, the steric shielding of the *Re* face of the enamine allows for an *Si*-facial nucleophilic attack of the π-allyl Pd species to give the desired (3*R*,4*S*) stereochemistry of **2a**.[3b,15]

In summary, a secondary amine- and Pd-catalyzed diastereoselective carbocyclization of aldehyde and ketone-tethered allenes has been developed. This dual catalytic cyclization reaction is efficient and broad in scope and has been extended to a catalytic asymmetric variant using diarylprolinol-based organocatalysts, affording substituted cyclopentane and pyrrolidine reaction products in up to 82% ee. Studies to probe the mechanism and origins of enantiocontrol, as well as other reactions requiring the cooperative action of organocatalysts and transition metal ions, are under active investigation in our laboratories and the results will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data for compounds **1**, **2a**−**2k**, **3a**−**3c**, **3f**, and **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) For reviews of cycloisomerization reactions, see: (a) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954–1993. (b) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899–2919. For examples of enallene cycloisomerization, see: (c) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 5231–5233. (d) Närhi, K.; Franzén, J.; Bäckvall, J. E. *Chem.—Eur. J.* **2005**, *11*, 6937–6943.

(14) For an organo-SOMO catalyzed mechanism of intramolecular allylation of aldehydes, see: Pham, P. V.; Ashton, K.; MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 1470–1473.

(15) (a) Seebach, D.; Grošelj, U.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2008**, *91*, 1999–2034. (b) Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. *Helv. Chim. Acta* **2009**, *92*, 1225–1259. (c) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *J. Am. Chem. Soc.* **2011**, *133*, 7065–7074.

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