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Pd-Catalyzed Acyl C–O Bond Activation for Selective Ring-Opening of *α*-Methylene-*β*-lactones with Amines

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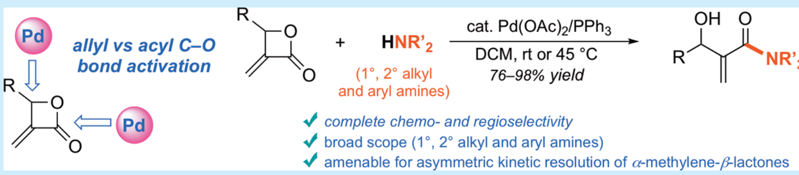
Supporting Information



ABSTRACT: A Pd-catalyzed ring-opening of *β*-lactones with various types of amines (primary, secondary, and aryl) to provide *β*-hydroxy amides with excellent selectivity toward acyl C–O bond cleavage is reported. The utility of this protocol is demonstrated in an asymmetric kinetic resolution providing enantioenriched *α*-methylene-*β*-lactones.

β-Lactones are important intermediates in organic synthesis.[1] They can be readily accessed in high enantiomeric purity, and they undergo a broad range of transformations, providing highly functionalized products. As part of our interest in the utility of *β*-lactones or *β*-lactone-derived strained heterocycles in organic synthesis, we have reported several of their reactions in the presence of transition-metal (TM) catalysts.[2] In particular, we reported that *α*-methylene-*β*-lactones **1** readily undergo cross-metathesis reactions[2e] and recently used this to access a focused library of 3,4-disubstituted *β*-lactones for proteomic profiling.[2c,d] A current interest is to develop further useful methods employing **1**, especially applications involving ring-opening reactions.

The ring-opening of *β*-lactones with different nucleophiles has been utilized in the synthesis of biologically important synthetic and natural products. Nevertheless, a major problem in opening *β*-lactones can be the formation of two isomeric products due to competing alkyl C–O and acyl C–O bond cleavages (Figure 1A).[1a] In particular, the selective opening of *β*-lactones with amines has proven to be challenging.[3] We hypothesized that *α*-methylene-*β*-lactones **1** could undergo selective ring opening with amine nucleophiles under Pd catalysis (Figure 1B). These unsaturated *β*-lactones could be expected to undergo allyl C–O bond activation with Pd to provide palladacycle **A**[4] (Figure 1B, path a). Alternatively, the olefin could act as a directing group[5] to facilitate the oxidative addition of Pd into the acyl C–O bond to form palladacycle **B** (Figure 1B, path b). Herein, the development of a Pd-catalyzed activation of *α*-methylene-*β*-lactones to provide solely *β*-hydroxy-*α*-methyleneamides in good to excellent yields is reported. The broad scope of the transformation using various *β*-lactones and amines is described.

As mentioned above, we postulated that selective opening of *α*-methylene-*β*-lactones might be promoted by oxidative addition of a TM into either the alkyl or acyl C–O bond. There is direct precedent for alkyl C–O bond activation of *β*-lactones. Puddephatt reported the oxidative addition of oxetan-2-one with a stoichiometric amount of a Pt complex via alkyl C–O cleavage (Figure 2).[6] Noels described a Pd-catalyzed opening of vinyl-substituted *β*-lactones to form butadiene acids.[7] This transformation was proposed to involve allyl C–O bond activation to form a palladalactone, which then undergoes *β*-hydride elimination. This mode of activation was utilized by Hattori with vinyl *β*-lactones generated in situ from the reaction of ketene with *α*,*β*-unsaturated aldehydes.[8] These allylic systems would appear to be especially relevant to an expectation that Pd catalysis might be used for allyl C–O bond cleavage in *α*-methylene-*β*-lactones.

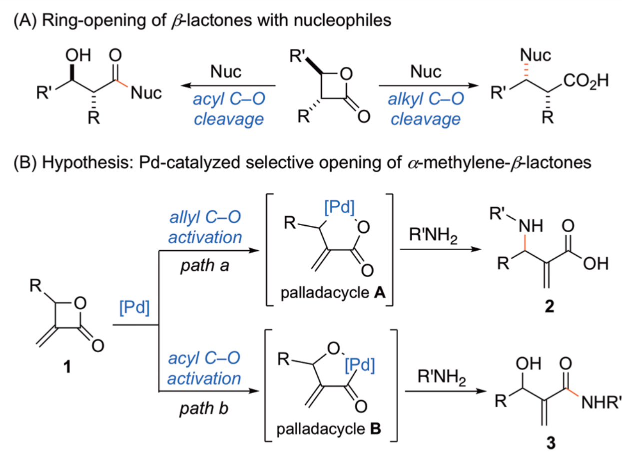


Figure 1. Alkyl vs acyl C–O bond cleavage in *β*-lactones.

There are, to our knowledge, no reports of TM-catalyzed ring opening of *β*-lactones at the acyl C–O bond. Consequently we looked into TM-catalyzed coupling of esters

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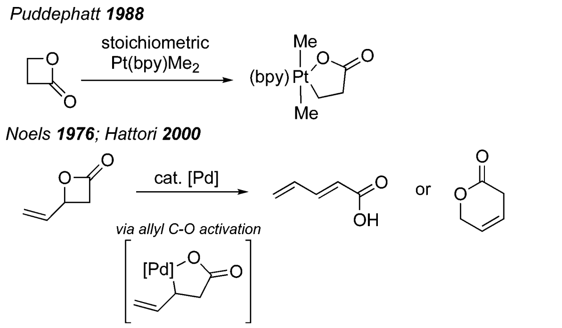


Figure 2. Transition-metal activation of alkyl C–O bonds in β-lactones.

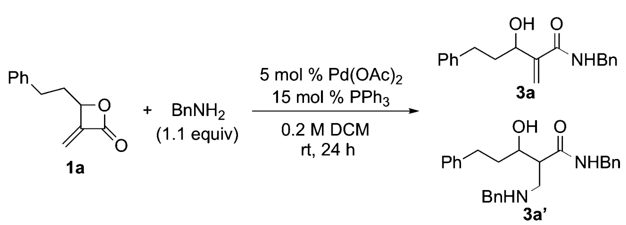
with amines. Certain types of esters, activated with α-aromatic/heteroaromatic or CF_3 substituents or certain alkoxy moieties, have been shown to undergo TM-catalyzed acyl C–O bond activation. The intermediates can be cross-coupled to form ketones[9] or undergo decarbonylation[10] before reductive coupling. Of potential direct relevance, Bao and co-workers recently developed a Pd-catalyzed amidation of activated esters that was believed to involve an acyl C–O insertion with a Pd catalyst.[11] Also, the Garg group utilized a nickel catalyst for the activation of aromatic methyl esters for amide formation.[12] We surmised that the α-methylene could play the role of an activating group for C–O insertion.

We initially probed the ring-opening of α-methylene-β-lactone **1a** with benzylamine in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 in DCM at rt (Table 1). The use of 2 equiv of benzylamine provided a 4:1 mixture of β-hydroxy amides **3a** and **3a′** (entry 1). The latter was believed to arise from aza-Michael addition of the excess amine to product **3a**. After optimization of the concentration and of the molar ratio of benzylamine, **3a** was isolated in 92% yield (entry 2). At 45 °C, complete conversion was achieved after 12 h, providing **3a** in nearly quantitative yield. Other solvents, such as THF and $CHCl_3$, as well as biphosphine ligands (BINAP and SEGPHOS), gave outcomes similar to that of entry 2. Other Pd sources (entries 4–6) also promoted the transformation. Notably, the use of catalytic $Pd(PPh_3)_4$ without exogenous phosphine ligand provided an efficient conversion, but **3a** and **3a′** were formed in a 10:1 ratio. When the reaction was carried out in the absence of Pd catalyst or phosphine ligand (entries 7–9), no significant conversion was observed. It is also worth noting that the other possible product, β-amino acid **2** (Figure 1B, path a) was never observed. Consistent with our alternate hypothesis (Figure 1B, path b), these results indicate that the reaction is promoted by initial oxidative addition of Pd(0) to the acyl C–O bond of β-lactone **1**.

The optimized conditions shown in the reaction scheme in Table 1 were utilized for the ring-opening of several α-methylene-β-lactones with various types of amines. As highlighted in Scheme 1, primary, secondary, and allyl amines provided β-hydroxy amides **3a–f** in good to excellent yields. The outcome observed with morpholine (**3e**) is noteworthy. Adam and co-workers found that cyclic, secondary amines (such as piperidine and pyrrolidine) reacted with α-methylene-β-lactones in the absence of a Pd catalyst to give conjugate addition products.[13]

Aryl amines were also successfully coupled to give exclusively the corresponding amides. When these amines were used in excess (2–4 equiv) and the reaction was conducted at 45 °C, β-hydroxy-α-methylene arylamides **3g–j** were obtained in high yields.

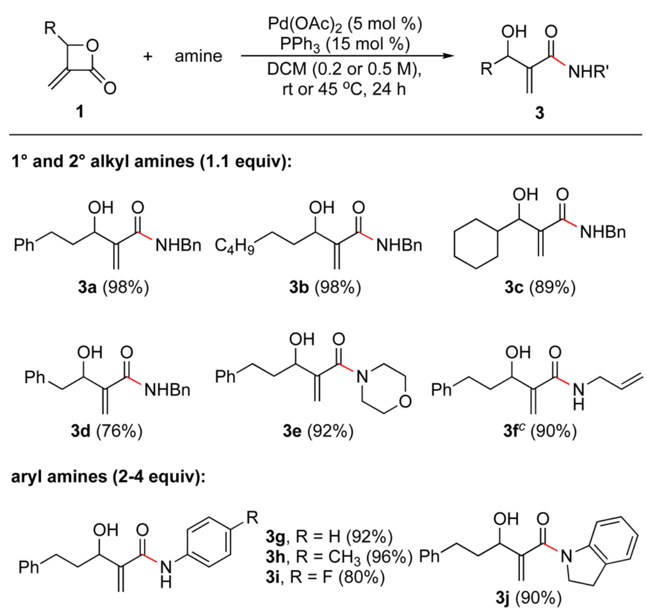
Table 1. Initial Studies on the Pd-Catalyzed Amidation of β-Lactone 1a with Benzylamine[a]



entry	variation from general conditions	ratio 3a:3a′[b]	yield of 3a[c] (%)
1	2 equiv of $BnNH_2$, 0.5 M	4:1	80
2	none	>20:1	92
3	45 °C, 12 h	>20:1	98
4	2 mol % $[Pd(allyl)Cl]_2$; 12 mol % PPh_3	>20:1	90[d]
5	2 mol % $Pd_2(dba)_3$; 12 mol % PPh_3	>20:1	95[d]
6	5 mol % $Pd(PPh_3)_4$; no PPh_3	10:1	85[d]
7	5 mol % $Pd_2(dba_3)$; no PPh_3		nr[e]
8	no $Pd(OAc)_2$		<5 conv[b]
9	no PPh_3		~10 conv[b]

[a]General conditions: 0.1 mmol of **1a**, benzylamine (1.1 equiv), Pd catalyst (5 mol % $Pd(OAc)_2$), 15 mol % of PPh_3 in DCM (0.2 M) at rt for 24 h. [b]Ratios and conversions were estimated by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yields except where noted. [d]^1H NMR yields using 1,3,5-trimethoxybenzene as internal standard. [e]The starting material was recovered; Pd black was observed on the wall of the reaction tube.

Scheme 1. Scope of Pd-Catalyzed Amidation of α-Methylene-β-lactones[a] **with Various Amines**[b]



[a]For the syntheses of the α-methylene-β-lactones, see the Supporting Information. [b]General conditions: 0.1–0.2 mmol of **1** (1 equiv), amine (1.1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (15 mol %) in DCM (0.2 M) at rt or 45 °C for 24 h. For aryl amines: 2–4 equiv of aryl amine was used in DCM (0.5 M) at 45 °C. [c]1.0 mmol scale.

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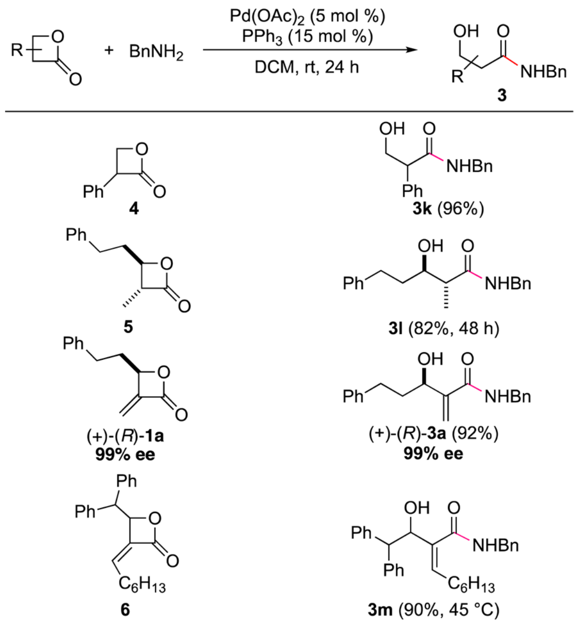
To extend the generality of this method, we next explored whether the Pd-catalyzed ring-opening can be used for simple β-lactones. As shown in Scheme 2, α-phenyl-β-lactone **4** underwent facile ring-opening with benzylamine, providing the ring-opened product in excellent yield at rt. Racemic *trans*-disubstituted β-lactone **5** also gave the desired product with complete selectivity, albeit in slightly lower yield. Notably, when β-lactone **4** or **5** was reacted with benzylamine in the absence of a Pd catalyst, the reaction was messier (based on ^{1}H NMRs of crude reaction mixtures), and the isolated yield for **3k** (65%) or **3l** (52%) was lower. Homochiral β-lactone (*R*)-**1a** (99% ee) also underwent ring opening to yield β-hydroxy amide (*R*)-**3a** (99% ee) without erosion of the stereochemical integrity. Likewise, α-alkylidene-β-lactone **6**, prepared by the Ru-catalyzed cross-metathesis of its corresponding α-methylene-β-lactone,[2e] provided α-alkylidene-β-hydroxy amide with complete retention of olefin geometry.

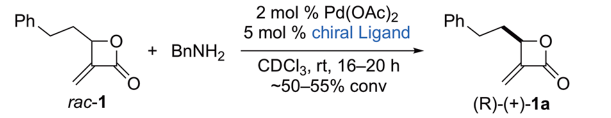
Scheme 2. Scope of Pd-Catalyzed Amidation of Various Types of β-Lactones[a]



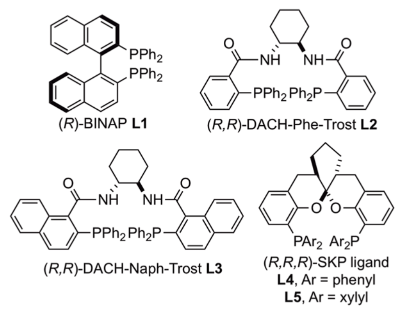
[a]For the syntheses of the β-lactones, see the Supporting Information. General conditions: 0.2 mmol of **1** (1 equiv), amine (1.1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (15 mol %) in DCM (0.2 M) at rt or 45 °C for 24 h.

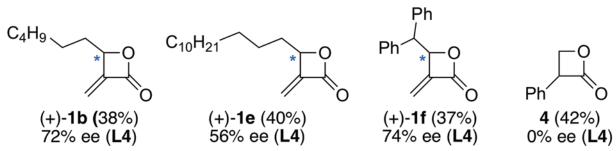
To date, enantioenriched α-methylene-β-lactones **1** have only been accessed via enzymatic kinetic resolution.[14] Our interest in α-methylene-β-lactones **1** as privileged intermediates in organic synthesis led us to explore the Pd-catalyzed amidation for potential resolution of racemic β-lactones. Several chiral phosphine ligands typically used in asymmetric Pd-catalyzed C−N bond coupling reactions were evaluated (Scheme 3). Racemic β-lactone **1a** underwent efficient amidation. Reactions were monitored by ^{1}H NMR analysis and were quenched after obtaining ∼50−55% conversions, typically after 16−20 h. (*R*)-BINAP and (*R*)-SEGPhos (not shown) did not provide any selectivity. When chiral Trost ligands[15] **L2** and **L3** were utilized, 5−38% ee's were obtained. The use of chiral spiroketal phosphine (SKP) ligands, recently developed by Ding and co-workers,[16] provided improved resolution, up to 68% ee (using SKP-**L4**). Further optimization

Scheme 3. Pd-Catalyzed Asymmetric Kinetic Resolution of β-Lactones[a]



ligand	yield (+)-**1a**	% ee
L1	40%	0
L2	38%	5 (*R*)
L3	42%	38 (*R*)
L4	43%	68 (*R*)
L5	46%	40 (*R*)





[a]General conditions: 0.1 to 0.2 mmol **1** (1 equiv), amine (1 equiv), $Pd(OAc)_2$ (2 mol %), chiral ligand (5 mol %) in $CDCl_3$ (0.2 M) at rt for 16−20 h.

(such as the use of various Pd sources, solvents, type and amounts of amine, reaction concentration, and temperature) did not improve the enantioselectivities. The conditions developed above for Pd-catalyzed asymmetric kinetic resolution were utilized for other β-lactones. With the exception of α-phenyl-β-lactone **4**, good yields and moderate enantioselectivities were obtained.

In conclusion, we have developed a highly selective Pd-catalyzed ring opening of α-methylene-β-lactones and β-lactones with various types of amines (primary, secondary, and aryl) to give amides via acyl C−O activation. The complete chemoselectivity and efficiency of the transformation are remarkable. Moreover, enantioenriched α-methylene-β-lactones can be obtained through kinetic resolution by using chiral phosphine ligands. The kinetic resolution of α-methylene-β-lactones has previously only been achieved by an enzymatic process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00494.

Detailed experimental procedures, analytical and spectral data for all new compounds, and HPLC traces for kinetic resolution experiments (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews see: (a) Nelson, S. G.; Dura, R. D.; Peelen, T. J. *Org. React.* **2012**, *82*, 471. (b) Romo, D.; Wang, Y.; Tennyson, R. L. *Heterocycles* **2004**, *64*, 605. (c) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545. (d) Schneider, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 744. (e) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403.

(2) (a) Malapit, C. A.; Howell, A. R. *J. Org. Chem.* **2015**, *80*, 8489. (b) Malapit, C. A.; Chitale, S. M.; Thakur, M. S.; Taboada, R.; Howell, A. R. *J. Org. Chem.* **2015**, *80*, 5196. (c) Camara, K.; Lasota, C. C.; Kamat, S. S.; Cravatt, B. F.; Howell, A. R. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 317. (d) Kamat, S. S.; Camara, K.; Parsons, W. H.; Chen, D.-H.; Dix, M. M.; Bird, T. D.; Howell, A. R.; Cravatt, B. F. *Nat. Chem. Biol.* **2015**, *11*, 164. (e) Raju, R.; Howell, A. R. *Org. Lett.* **2006**, *8*, 2139.

(3) For selected examples, see: (a) Wiedemann, E. H.; Mandl, F. A.; Blank, I. D.; Ochsenfeld, C.; Ofial, A. R.; Sieber, S. A. *ChemPlusChem* **2015**, *80*, 1673. (b) Noel, A.; Delpech, B.; Crich, D. *Org. Biomol. Chem.* **2012**, *10*, 6480. (c) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308. (d) Ratemi, E. S.; Vederas, J. C. *Tetrahedron Lett.* **1994**, *35*, 7605. (e) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1326. (f) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105.

(4) For the intermediacy of an α-alkylidenepallada-γ-lactone, see: Choi, J.-C.; Shiraishi, K.; Takenaka, Y.; Yasuda, H.; Sakakura, T. *Organometallics* **2013**, *32*, 3411.

(5) (a) Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 2084. (b) Gandeepan, P.; Cheng, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 5738. (c) Yamada, S.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1194.

(6) (a) Aye, K.-T.; Colpitts, D.; Ferguson, G.; Puddephatt, R. J. *Organometallics* **1988**, *7*, 1454. (b) Aye, K.-T.; Gelmini, L.; Payne, N. C.; Vittal, J. J.; Puddephatt, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 2464.

(7) Noels, A. F.; Herman, J. J.; Teyssie, P. *J. Org. Chem.* **1976**, *41*, 2527.

(8) (a) Hattori, T.; Suzuki, Y.; Uesugi, O.; Oi, S.; Miyano, S. *Chem. Commun.* **2000**, 73. (b) Hattori, T.; Suzuki, Y.; Ito, Y.; Hotta, D.; Miyano, S. *Tetrahedron* **2002**, *58*, 5215.

(9) For selected examples of TM-catalyzed acyl C−O bond activation of esters, see: (a) Ben Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Newman, S. G. *J. Am. Chem. Soc.* **2017**, *139*, 1311. (b) Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 5615.

(10) For selected examples of TM-catalyzed activation of esters with decarbonylation, see: (a) Muto, K.; Hatakeyama, T.; Itami, K.; Yamaguchi, J. *Org. Lett.* **2016**, *18*, 5106. (b) Pu, X.; Hu, J.; Zhao, Y.; Shi, Z. *ACS Catal.* **2016**, *6*, 6692. (c) Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508. (d) LaBerge, N. A.; Love, J. A. *Eur. J. Org. Chem.* **2015**, 5546. (e) Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371.

(11) Bao, Y. S.; Zhaorigetu, B.; Agula, B.; Baiyin, M. H.; Jia, M. L. *J. Org. Chem.* **2014**, *79*, 803.

(12) Hie, L.; Fine Nathel, N. F.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Garg, N. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 2810.

(13) Adam, W.; Nava-Salgado, V. O. *J. Org. Chem.* **1995**, *60*, 578.

(14) Adam, W.; Groer, P.; Saha-Möller, C. R. *Tetrahedron: Asymmetry* **1997**, *8*, 833.

(15) (a) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968.

(16) (a) Wang, X.; Guo, P.; Han, Z.; Wang, X.; Ding, K. *J. Am. Chem. Soc.* **2014**, *136*, 405. (b) Wang, X.; Meng, F.; Wang, Y.; Han, Z.; Chen, Y.; Liu, L.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9276.

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