ChemPubSoc Europe

DOI: 10.1002/chem.201406135

CHEMISTRY
A European Journal
Communication

Lewis Acid Catalysis

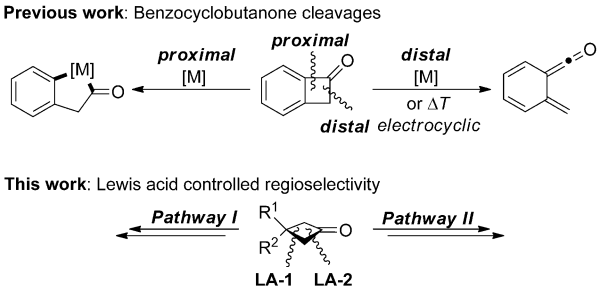
Regiodivergent Cyclobutanone Cleavage: Switching Selectivity with Different Lewis Acids

Laetitia Souillart and Nicolai Cramer*[a]

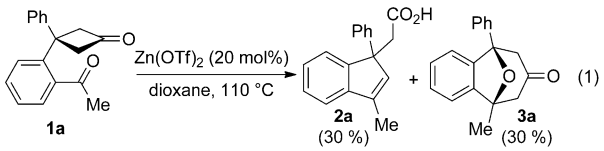
Abstract: The exploitation of strain release in small rings as driving force to enable complex transformations is a powerful synthetic tool. Among them, cyclobutanones are particularly versatile substrates that can be elaborated in a wide variety of structurally diverse building blocks. Herein, Lewis acid catalyzed rearrangement reactions are presented that provide selective access to two structurally distinct polycyclic scaffolds, that is, indenylacetic acid derivatives and benzoxabicyclo[3.2.1]octan-3-ones. The choice of the Lewis acid fully controls the reaction pathway and the regioselectivity of the cyclobutanone C–C bond cleavage site.

The exploitation of strain release in small rings as driving force to enable synthetic transformations has received considerable attention.[1] Among them, cyclobutane derivatives are versatile substrates that can be elaborated in a wide variety of structurally diverse building blocks.[2–6] Mostly, the site of the C–C bond cleavage is inherently substrate controlled. Recently, catalytic asymmetric C–C bond cleavages enabling a selection between the enantiotopic C–C bonds have been reported.[7–9] On the other hand, a regiodivergent cleavage of the proximal and distal C–C bond of a four-membered ring would enable access to two structurally different products. For example, a regiodivergent ring opening of benzocyclobutanones was achieved by using transition-metal catalysts[10–12] or by a thermally induced electrocyclic ring opening (Scheme 1).[13] Preferably, such a reactivity switch can be triggered by two different catalysts under otherwise identical reaction conditions.[14] Herein, we report a Lewis acid catalyzed ring opening of cyclobutanones. Depending on the nature of the Lewis acid, two complementary reaction pathways are triggered, leading to two different scaffolds as a result of either a proximal or distal C–C bond cleavage of the cyclobutanone.

Initially, cyclobutanone **1a** was exposed to 20 mol% $Zn(OTf)_2$ and two distinct products **2a** and **3a** that underwent a complete skeletal rearrangement were isolated in moderate yields [Eq. (1)].



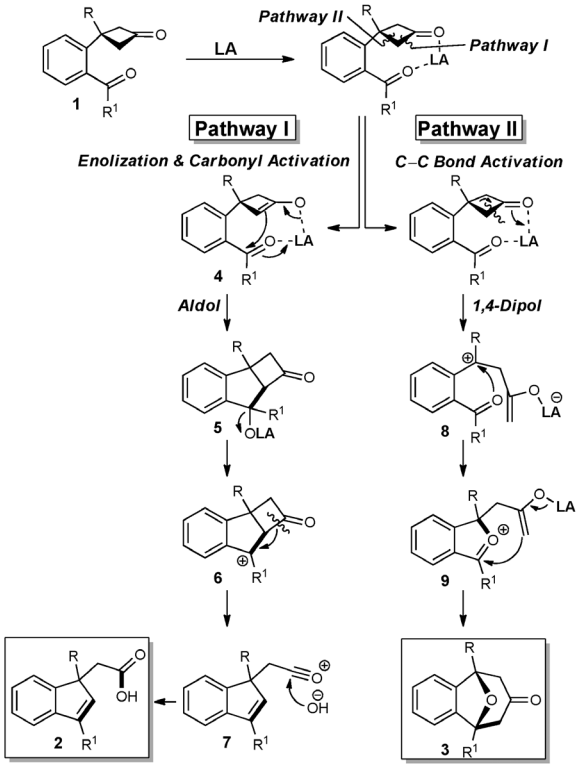
Scheme 1. Regiodivergent cyclobutanone C–C bond cleavages.



Mechanistically, this intriguing transformation might be rationalized by the following pathways. Initial coordination of the Lewis acid to the carbonyl group of the cyclobutanone can trigger two reaction cascades, depending on the nature of the Lewis acid used (Scheme 2). "Soft" metals trigger an enolization reaction to give **4** (pathway I). Subsequent aldol addition across the appended carbonyl group provides intermediate **5**. Under the reaction conditions, ionization would then lead to benzylic carbenium ion **6**, which in turn would be prone to a strain-driven retro-Friedel–Crafts acylation, forming an olefin and a highly reactive acylium cation **7**. The reaction is terminated by nucleophilic trapping of the acylium species, either by water generated in the reaction or by an added nucleophile, giving rise to indenylacetic acid derivative **2**. In the complementary reaction pathway II, the coordination of a "hard" Lewis acid induces a heterolytic ring-opening reaction of the cyclobutanone core, delivering 1,4-dipol **8**. The propensity of such a ring opening strongly depends on the substituents stabilizing the arising benzylic carbenium ion.[15] This behavior is known for strongly polarized donor–acceptor cyclobutanes having either powerful donors, such as an alkoxy group[16] or a Nicholas-type complexed alkyne,[17] that are able to sufficiently stabilize the arising carbenium ion or an acidic malonate pattern[18] to strongly stabilize the anion. Systems that would

[a] L. Souillart, Prof. Dr. N. Cramer
Laboratory of Asymmetric Catalysis and Synthesis
EPFL SB ISIC LCSA
BCH 4305, 1015 Lausanne (Switzerland)
Fax: (+41) 21 693 97 00
E-mail: Nicolai.cramer@epfl.ch
Homepage: http://isic.epfl.ch/lcsa

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201406135.



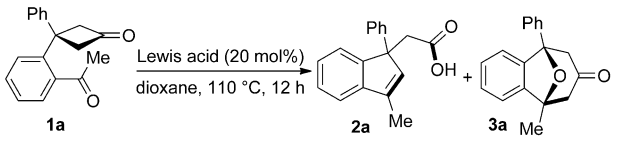
Scheme 2. Proposed mechanistic rationale for the regiodivergent C–C cleavage of cyclobutanones **1**.

open to simple ketone enolates and benzylic cations are much less prone to ring opening.[19] Intramolecular cyclization of **8** with the carbonyl oxygen atom would provide oxycarbenium ion **9**. In turn, **9** undergoes an intramolecular aldol cyclization, leading to the benzoxabicyclo[3.2.1]octan-3-one scaffold **3**, which overall can be viewed as a formal [4+2] cycloaddition. It would be highly desirable to selectively address either pathway by proper choice of the catalyst and the reaction conditions. Herein, we report the use of different Lewis acids to selectively trigger and switch between these two reaction pathways.[20,21]

The evaluation of the reaction conditions was initially performed on cyclobutanone **1a** as a model substrate, primarily examining the behavior of different Lewis acids on the selectivity (Table 1). In summary, copper(II) triflate as a soft Lewis acid was found to be an excellent catalyst for the aldol-addition pathway I, leading selectively to indenyl carboxylic acid **2a** in 80% isolated yield (entry 1). In contrast, zinc(II) triflate and zinc(II) chloride were both not selective and lead to a mixture of the products **2a** and **3a**, indicating that both pathways were operative (entries 2 and 3). On the other hand, both iron(III) chloride and titanium(IV) chloride exclusively gave rise to bicyclic ketone **3a**, albeit in moderate yields (entries 4 and 5). Scandium(III) triflate displayed an improved reactivity by selectively affording **3a** in a higher yield (entry 6). Finally, tin(IV) chloride was found to be the best catalyst, resulting in the formation of **3a** in 92% isolated yield (entry 7).[22]

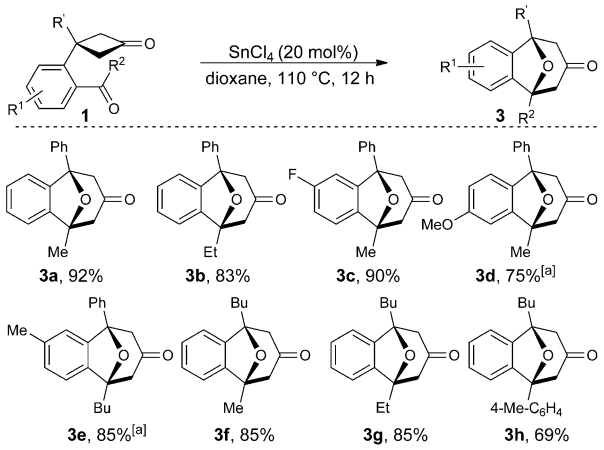
Having established two sets of conditions to selectively trigger both rearrangement pathways, we next investigated the generality and limitations of the two transformations. First, the

Table 1. Optimizations for a selective pathway switch between indenyl carboxylic acid **2a** and bicyclic ketone **3a**.[a]



Entry	Lewis acid	Yield of **2a** [%][b]	Yield of **3a** [%][b]
1	$Cu(OTf)_2$	**85 (80)**	0
2	$Zn(OTf)_2$	30	30
3	$ZnCl_2$	33	67 (64)
4	$FeCl_3$	0	55
5	$TiCl_4$	0	62
6	$Sc(OTf)_3$	0	**80 (72)**
7	$SnCl_4$	0	**95 (92)**

[a] Reaction conditions: **1a** (0.05 mmol) and Lewis acid (1.00 μmol) in dioxane (0.25 M) at 110 °C for 12 h; [b] determined by ^{1}H NMR spectroscopy (isolated yield).



Scheme 3. Scope of the synthesis of bicyclic ketones **3**. Conditions: **1** (0.10 mmol) and $SnCl_4$ (0.02 mmol) in dioxane (0.25 M) at 110 °C for 12 h; [a] $ZnCl_2$ instead of $SnCl_4$.

cleavage pathway initiating the formation of benzoxabicyclo[3.2.1]octan-3-one **3** was exploited (Scheme 3). The nature of the rearranged product was confirmed by X-ray crystallography of product **3b** (Figure 1). The electronic properties of the aromatic tether can be varied and both electron-withdrawing and -donating groups (**3c** and **3d**) are well tolerated to provide the oxabicyclooctanones **3** in reliably high yields. Besides aromatic substituents R′, which provide a good stabilization of intermediate **8** via a dibenzylic carbenium ion, 3-alkyl-substituted cyclobutanones **1e–h** are also competent substrates. This is worth noting, because the intermediate carbenium ions are less stabilized, which might impact the ring-opening rates significantly. Pleasingly, this substrate type still efficiently rearranged into ketones **3e–h**. However, substrates having an aldehyde moiety instead of a ketone are not competent substrates, owing to their higher carbonyl electrophilicity.

Next, we turned our attention towards the second rearrangement pathway, exploiting the formation of indenylacetic

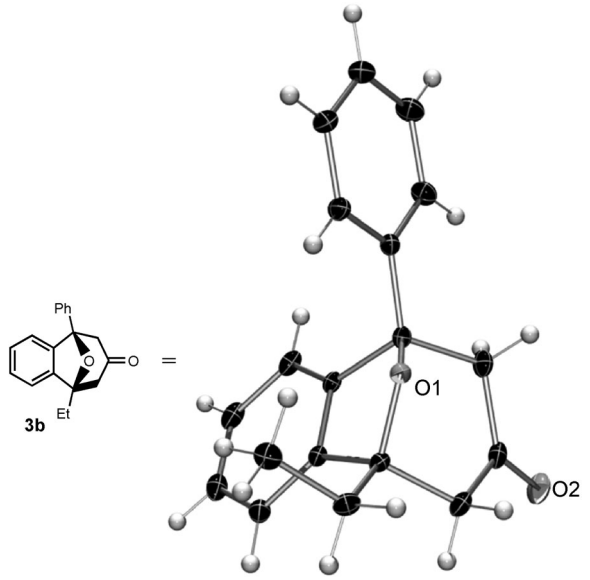
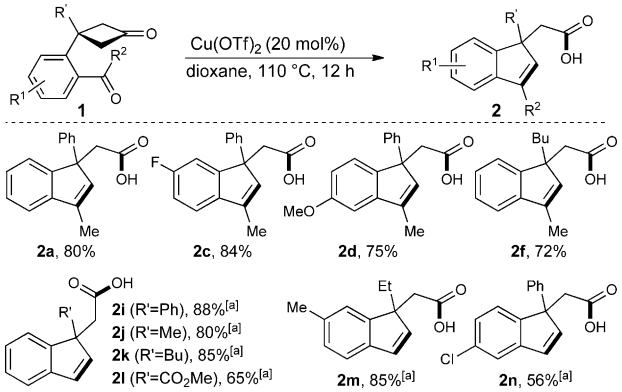
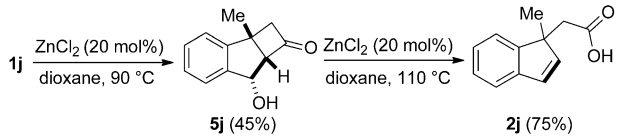


Figure 1. X-ray crystal structure of ketone **3b**.



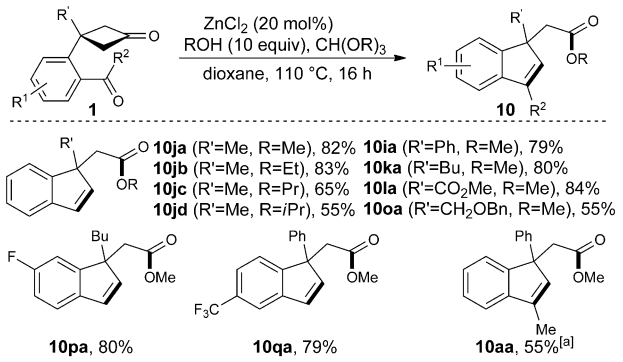
Scheme 4. Scope of the synthesis of indenyl derivatives **2**. Conditions: **1** (0.10 mmol) and $Cu(OTf)_2$ (0.02 mmol) in dioxane (1 M) at 110 °C for 16 h; [a] $ZnCl_2$ instead of $Cu(OTf)_2$.



Scheme 5. Stepwise formation of carboxylic acid **2j** supports proposed aldol intermediate **5j**.

is a transient intermediate in the reaction. Furthermore, this suggests that the high reaction temperature is required for the ionization or the retro-Friedel–Crafts step. On the other hand, an increased reaction temperature of 130 °C led to significant product degradation, thus leaving a rather narrow optimal temperature window. Moreover, submission of **5a** to tin(IV) chloride in refluxing dioxane only lead to the formation of indenyl acetic acid **2a**, indicating that the steps after the aldolization are independent of the hard or soft nature of the Lewis acid.

With this additional information on the mechanism in hand (Scheme 6), we further explored trapping the acylium ion spe-



Scheme 6. Synthesis of indenyl esters **10** by trapping of reactive intermediates with added nucleophiles. Conditions: **1** (0.10 mmol) and $ZnCl_2$ (0.02 mmol) in dioxane (1 M) at 110 °C for 16 h; [a] $Cu(OTf)_2$ instead of $ZnCl_2$.

acids **2** (Scheme 4). With catalytic amounts of copper(II) triflate as Lewis acid, cyclobutanones **1** bearing a ketone moiety rearranged smoothly into indenylacetic acids **2** bearing a trisubstituted double bond. The reaction is not influenced by electronic modifications of the aromatic tether (**2c** and **2d**). The use of aldehyde-containing substrates **1** (R^2 = H) enabled the use of zinc(II) chloride, providing equally good reactivities and yields (**3i**–**m**). Different substituents on the cyclobutanone ring including esters are well tolerated and carboxylic acids **2** were obtained in good yields. Modifications of the electronic properties of the aromatic moiety did not influence the selectivity, although a *meta*-chlorine substituent (**2n**) diminished the yield.

To gain valuable insights on the rearrangement process, we tried to identify reactive intermediates. Indeed, the expected intermediate aldol product **5j** could be isolated as a single diastereomer in moderate yield by lowering the reaction temperature to 90 °C (Scheme 5). Resubmission of **5j** to the standard reaction conditions formed indenylacetic acid, proving that **5j** cies with external nucleophiles that are added to the reaction mixture. For example, the corresponding indenyl esters **10** were directly obtained by adding the corresponding alcohol. To suppress the formation of the carboxylic acid by-product **2**, formed by the reaction with generated water, orthoformates were added as water scavengers. In this respect, several alcohols were well suited. Particularly, simple primary alcohols such as methanol, ethanol, or propanol deliver the corresponding esters in good yields. The more sterically hindered isopropanol afforded the isopropyl ester, albeit in a lower yield. Similar to the scope without added nucleophiles, this variant is tolerant to a wide scope of substrates with different steric and electronic substrate variations.

In summary, we have demonstrated that the inherent ring strain of cyclobutanone can be exploited with Lewis acid catalysts, giving access to rearranged and synthetically valuable building blocks. One of the most prominent features is the switch of the reaction pathways of enolization or ionization by proper choice of the Lewis acid, allowing a regiodivergent

cleavage of the cyclobutane C–C bond. On the one hand, indenylacetic acid derivatives can be obtained selectively with copper triflate and, complementarily, benzoxabicyclo[3.2.1]octan-3-one are accessible by using tin tetrachloride as catalyst. Further work aims at introducing enantiocontrol in the cleavage reaction.

Experimental Section

Indenylacetic acid 2a

Cyclobutanone **1a** (26.4 mg, 0.100 mmol) and copper(II) triflate (7.2 mg, 0.020 mmol) were weighed in an oven-dried vial equipped with a magnetic stir bar, capped with a septum, and purged with nitrogen. Then, dry dioxane (0.1 mL) was added. The mixture was stirred for 20 min at 23 °C and subsequently heated to 110 °C. After 16 h, the reaction mixture was cooled to 23 °C and purified by silica-gel column chromatography eluting with pentane/ethyl acetate (4:1). Indenyl carboxylic acid **2a** was isolated as colorless oil in 80% yield (21 mg).

Benzoxabicyclo[3.2.1]octan-3-one 3a

Cyclobutanone **1a** (26.4 mg, 0.100 mmol) was weighed in an oven-dried vial equipped with a magnetic stir bar, capped with a septum, and purged with nitrogen. Dry dioxane (0.4 mL) and tin(IV) chloride (2.3 μL, 0.020 mmol) were added. The mixture was stirred for 20 min at 23 °C and subsequently heated to 110 °C. After 16 h, the reaction mixture was cooled to 23 °C and purified by silica-gel column chromatography eluting with pentane/ethyl acetate (10:1). Benzoxabicyclo[3.2.1]octan-3-one **3a** was isolated as white solid in 92% yield (24 mg).

Acknowledgements

This work is supported by the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement n° 257891. We thank Dr. R. Scopelliti for X-ray crystallographic analysis of **3b**.

Keywords: cyclobutanones · Lewis acids · rearrangement · regiodivergence · ring-opening reactions

[1] For selected reviews, see: a) J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485 – 1538; b) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610 – 618; c) T. Seiser, N. Cramer, *Org. Biomol. Chem.* **2009**, *7*, 2835 – 2840; d) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2011**, *50*, 7740 – 7752; *Angew. Chem.* **2011**, *123*, 7884 – 7896; e) C. Aïssa, *Synthesis* **2011**, 3389 – 3407; f) M. Murakami, T. Matsuda, *Chem. Commun.* **2011**, *47*, 1100 – 1105.

[2] For recent homologation reactions of cyclobutanones, see: a) D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878 – 879; b) J. A. Dabrowski, D. C. Moebius, A. J. Wommack, A. F. Kornahrens, J. S. Kingsbury, *Org. Lett.* **2010**, *12*, 3598 – 3601; c) V. L. Rendina, D. C. Moebius, J. S. Kingsbury, *Org. Lett.* **2011**, *13*, 2004 – 2007.

[3] For examples of Brønsted acid catalyzed rearrangements of cyclobutanols, see: a) B. M. Trost, D. W. C. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 12541 – 12554; b) Q. W. Zhang, C. A. Fan, H. J. Zhang, Y. Q. Tu, Y. M. Zhao, P. Gu, Z. M. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 8572 – 8574; *Angew. Chem.* **2009**, *121*, 8724 – 8726; c) E. Zhang, C. A. Fan, Y. Q. Tu, F. M. Zhang, Y. L. Song, *J. Am. Chem. Soc.* **2009**, *131*, 14626 – 14627.

[4] For examples of Pd-catalyzed rearrangements of cyclobutanols through 1,2-shift, see: a) G. R. Clark, S. Thiensathit, *Tetrahedron Lett.* **1985**, *26*, 2503 – 2506; b) H. Nemoto, M. Yoshida, K. Fukumoto, *J. Org. Chem.* **1997**, *62*, 6450 – 6451; c) H. Nemoto, J. Miyata, M. Yoshida, N. Raku, K. Fukumoto, *J. Org. Chem.* **1997**, *62*, 7850 – 7857; d) M. Yoshida, H. Nemoto, M. Ihara, *Tetrahedron Lett.* **1999**, *40*, 8583 – 8586; e) M. Yoshida, K. Sugimoto, M. Ihara, *Tetrahedron Lett.* **2000**, *41*, 5089 – 5092; f) R. C. Larock, C. K. Reddy, *Org. Lett.* **2000**, *2*, 3325 – 3327; g) M. Yoshida, K. Sugimoto, M. Ihara, *Tetrahedron* **2002**, *58*, 7839 – 7846; h) M. Yoshida, K. Sugimoto, M. Ihara, *Org. Lett.* **2004**, *6*, 1979 – 1982; i) A. Schweinitz, A. Chtchemelinine, A. Orellana, *Org. Lett.* **2011**, *13*, 232 – 235; Ru-catalyzed: j) M. Yoshida, K. Sugimoto, M. Ihara, *Tetrahedron Lett.* **2001**, *42*, 3877 – 3880; k) K. Sugimoto, M. Yoshida, M. Ihara, *Synlett* **2006**, 1923 – 1927; Au-catalyzed: l) J. P. Markham, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 9708 – 9709.

[5] For examples of achiral β-carbon elimination from cyclobutanols, see: a) T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **1999**, *121*, 11010 – 11011; b) T. Nishimura, K. Ohe, S. Uemura, *J. Org. Chem.* **2001**, *66*, 1455 – 1465; c) N. Ishida, S. Sawano, M. Murakami, *Chem. Commun.* **2012**, *48*, 1973 – 1975; d) N. Ishida, Y. Nakanishi, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 11875 – 11878; *Angew. Chem.* **2013**, *125*, 12091 – 12094; e) N. Cramer, T. Seiser, *Synlett* **2011**, 449 – 460.

[6] For examples of achiral Rh-catalyzed cyclobutanone C–C bond cleavages, see: a) M. Murakami, H. Amii, Y. Ito, *Nature* **1994**, *370*, 540 – 541; b) M. Murakami, H. Amii, K. Shigeto, Y. Ito, *J. Am. Chem. Soc.* **1996**, *118*, 8285 – 8290; c) M. Murakami, K. Takahashi, H. Amii, Y. Ito, *J. Am. Chem. Soc.* **1997**, *119*, 9307 – 9308; d) M. Murakami, T. Tsuruta, Y. Ito, *Angew. Chem. Int. Ed.* **2000**, *39*, 2484 – 2486; *Angew. Chem.* **2000**, *112*, 2600 – 2602; e) M. Murakami, T. Itahashi, Y. Ito, *J. Am. Chem. Soc.* **2002**, *124*, 13976 – 13977; f) T. Matsuda, M. Makino, M. Murakami, *Org. Lett.* **2004**, *6*, 1257 – 1259; g) T. Matsuda, M. Shigeno, Y. Maruyama, M. Murakami, *Chem. Lett.* **2007**, *36*, 744 – 745; Ni-catalyzed: h) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 6932 – 6933; i) M. Murakami, S. Ashida, *Chem. Commun.* **2006**, 4599 – 4601; j) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2006**, *128*, 2166 – 2167; k) H. M. Ko, G. Dong, *Nat. Chem.* **2014**, *6*, 739 – 744; Pd-catalyzed: l) T. Matsuda, M. Shigeno, M. Murakami, *Org. Lett.* **2008**, *10*, 5219 – 5221; m) N. Ishida, W. Ikemoto, M. Murakami, *Org. Lett.* **2012**, *14*, 3230 – 3232; n) N. Ishida, W. Ikemoto, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 5912 – 5915.

[7] L. Souillart, E. Parker, N. Cramer, *Top. Curr. Chem.* **2014**, *346*, 163 – 193.

[8] For examples of asymmetric cyclobutanone C–C bond cleavages, see: a) L. Liu, N. Ishida, M. Murakami, *Angew. Chem.* **2012**, *124*, 2535 – 2538; *Angew. Chem. Int. Ed.* **2012**, *51*, 2485 – 2488; b) E. Parker, N. Cramer, *Organometallics* **2014**, *33*, 780 – 787; c) L. Souillart, E. Parker, N. Cramer, *Angew. Chem.* **2014**, *126*, 3045 – 3049; *Angew. Chem. Int. Ed.* **2014**, *53*, 3001 – 3005; d) L. Souillart, N. Cramer, *Angew. Chem.* **2014**, *126*, 9794 – 9798; *Angew. Chem. Int. Ed.* **2014**, *53*, 9640 – 9644.

[9] For examples of asymmetric cyclobutanol C–C bond cleavages, see: Pd-catalyzed: a) B. M. Trost, T. Yasukata, *J. Am. Chem. Soc.* **2001**, *123*, 7162 – 7163; b) T. Nishimura, Y. Matsumura, Y. Maeda, S. Uemura, *Chem. Commun.* **2002**, 50 – 51; c) Y. Matsumura, Y. Maeda, T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 8862 – 8869; d) B. M. Trost, J. Xie, *J. Am. Chem. Soc.* **2006**, *128*, 6044 – 6045; e) B. M. Trost, J. Xie, *J. Am. Chem. Soc.* **2008**, *130*, 6231 – 6242; Rh-catalyzed: f) T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379 – 3381; g) T. Matsuda, M. Shigeno, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12086 – 12087; h) T. Seiser, N. Cramer, *Angew. Chem. Int. Ed.* **2008**, *47*, 9294 – 9297; *Angew. Chem.* **2008**, *120*, 9435 – 9438; i) R. Shintani, K. Takatsu, T. Hayashi, *Org.Lett.* **2008**, *10*, 1191 – 1193; j) T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6320 – 6323; *Angew. Chem.* **2009**, *121*, 6438 – 6441; k) M. Shigeno, T. Yamamoto, M. Murakami, *Chem. Eur. J.* **2009**, *15*, 12929 – 12931; l) T. Seiser, N. Cramer, *Chem. Eur. J.* **2010**, *16*, 3383 – 3391; m) T. Seiser, N. Cramer, *J. Am. Chem. Soc.* **2010**, *132*, 5340 – 5342; n) T. Seiser, G. Cathomen, N. Cramer, *Synlett* **2010**, 1699 – 1703; o) T. Seiser, N. Cramer, *Angew. Chem. Int. Ed.* **2010**, *49*, 10163 – 10167; *Angew. Chem.* **2010**, *122*, 10361 – 10365; p) M. Waibel, N. Cramer, *Chem. Commun.* **2011**, *47*, 346 – 348; q) L. Souillart, N. Cramer, *Chem. Sci.* **2014**, *5*, 837 – 840; r) A. Yada, S. Fujita, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 7217 – 7220.

[10] For examples of proximal bond cleavages, see: a) A. Chtchemelinine, D. Rosa, A. Orellana, *J. Org. Chem.* **2011**, *76*, 9157 – 9162; b) T. Xu, G. Dong, *Angew. Chem.* **2012**, *124*, 7685 – 7689; *Angew. Chem. Int. Ed.* **2012**, *51*, 7567 – 7571; c) T. Xu, H. M. Ko, N. A. Savage, G. Dong, *J. Am. Chem. Soc.*

2012, *134*, 20005 – 20008; d) P.-h. Chen, T. Xu, G. Dong, *Angew. Chem.* **2014**, *126*, 1700 – 1704; *Angew. Chem. Int. Ed.* **2014**, *53*, 1674 – 1678; e) T. Xu, N. A. Savage, G. Dong, *Angew. Chem.* **2014**, *126*, 1922 – 1926; *Angew. Chem. Int. Ed.* **2014**, *53*, 1891 – 1895.

[11] For examples of distal bond cleavages, see: a) M. A. Huffman, L. S. Liebeskind, W. T. Pennington, *Organometallics* **1990**, *9*, 2194 – 2196; b) M. A. Huffman, L. S. Liebeskind, W. T. Pennington, *Organometallics* **1992**, *11*, 255 – 266.

[12] For DFT studies, see: L. Ding, N. Ishida, M. Murakami, K. Morokuma, *J. Am. Chem. Soc.* **2014**, *136*, 169 – 178.

[13] P. Schiess, M. Eberle, M. Huys-Francotte, J. Wirz, *Tetrahedron Lett.* **1984**, *25*, 2201 – 2204.

[14] For selected examples of Lewis acid catalyzed regio-divergent transformations, see: a) K. Ohmatsu, T. Tanaka, T. Ooi, K. Maruoka, *Tetrahedron* **2009**, *65*, 7516 – 7522; b) L. Liu, J. Zhang, *Angew. Chem. Int. Ed.* **2009**, *48*, 6093 – 6096; *Angew. Chem.* **2009**, *121*, 6209 – 6212; c) G. Righi, R. Antonioletti, R. Pelagalli, *Tetrahedron Lett.* **2012**, *53*, 5582 – 5584; d) G. Righi, G. Scotti, F. Caruso, M. Rossi, F. Mecozzi, R. Antonioletti, R. Pelagalli, *Tetrahedron* **2013**, *69*, 9557 – 9565; e) Y. Liu, J. Liu, Y. Huang, F-l. Qing, *Chem. Commun.* **2013**, *49*, 7492 – 7494.

[15] J. Matsuo, *Tetrahedron Lett.* **2014**, *55*, 2589 – 2595.

[16] a) R. Huisgen, L. A. Feiler, P. Otto, *Chem. Ber.* **1969**, *102*, 3405 – 3427; b) L. H. Dao, A. C. Hopkinson, E. Lee-Ruff, *Tetrahedron Lett.* **1978**, *19*, 1413 – 1414; c) P. Duperrouzel, E. Lee-Ruff, *J. Can. Chem.* **1980**, *58*, 51 – 54; d) J. Matsuo, S. Sasaki, H. Tanaka, H. Ishibashi, *J. Am. Chem. Soc.* **2008**, *130*, 11600 – 11601; e) J. Matsuo, S. Sasaki, T. Hoshikawa, H. Ishibashi, *Org. Lett.* **2009**, *11*, 3822 – 3825; f) J. Matsuo, S. Negishi, H. Ishibashi, *Tetrahedron Lett.* **2009**, *50*, 5831 – 5833; g) J. Matsuo, R. Okado, H. Ishibashi, *Org. Lett.* **2010**, *12*, 3266 – 3268.

[17] a) M. Kawano, T. Kiuchi, J. Matsuo, H. Ishibashi, *Tetrahedron Lett.* **2012**, *53*, 432 – 434; b) E. A. Allart, S. D. R. Christie, G. J. Pritchard, M. R. J. Elsegood, *Chem. Commun.* **2009**, 7339 – 7341.

[18] a) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 14202 – 14203; b) M. M. A. R. Moustafa, B. L. Pagenkopf, *Org. Lett.* **2010**, *12*, 4732 – 4735; c) A. C. Stevens, C. Palmer, B. L. Pagenkopf, *Org. Lett.* **2011**, *13*, 1528 – 1531; d) A. C. Stevens, C. Palmer, B. L. Pagenkopf, *Org. Lett.* **2010**, *12*, 4736 – 4738; R. Okado, A. Nowaki, J. I. Matsuo, H. Ishibashi, *Chem. Pharm. Bull.* **2012**, *60*, 21 – 22; e) N. Vemula, A. C. Stevens, T. B. Schon, B. L. Pagenkopf, *Chem. Commun.* **2014**, *50*, 1668 – 1670.

[19] a) V. P. Abegg, A. C. Hopkinson, E. Lee-Ruff, *J. Can. Chem.* **1978**, *56*, 99 – 103; b) R. D. Miller, D. R. McKean, *Tetrahedron Lett.* **1979**, *20*, 1003 – 1006; c) R. D. Miller, D. R. McKean, *Tetrahedron Lett.* **1980**, *21*, 2639 – 2642; d) J. Matsuo, K. Harada, M. Kawano, H. Ishibashi, *Org. Lett.* **2011**, *13*, 5986 – 5989.

[20] The term "regio-divergent" is used in a formal sense to indicate the different product branches with respect to the substrate and has no implications on the reaction mechanism.

[21] Another possible but unlikely mechanism under the strictly anhydrous reaction conditions would comprise the addition of water to the carbonyl group of **5**, followed by E1cb elimination.

[22] Preliminary attempts for an asymmetric reaction were either hampered by sluggish reactivity or non-existing enantiodiscrimination using chiral ligands (Cu^{II} BOX/PyBOX complexes or TRIP as a chiral Bronsted acid).

Received: October 18, 2014
Published online on December 4, 2014