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(+)-Camphor- Mediated Kinetic Resolution of Allylalanes: A Strategy Towards Enantio-Enriched Cyclohex-2-en-1-ylalane

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An efficient (+)-camphor-mediated kinetic resolution of racemic cyclohex-2-en-1-ylalane is described. This approach provides an enantiomerically enriched form of the alane, *in-situ* available for synthetic uses. Applied to the allylation of aldehydes, this protocol leads to the corresponding homoallylalcohols in a highly enantioselective manner.

Configurationally stable organometallic compounds are traditionally difficult to generate and to handle and are confined to a limited number of metals. In this context, the enantioselective generation of a chiral nucleophilic organometallic species is a very fascinating and challenging approach in asymmetric synthesis.[1] Among synthetically useful organometallic reagents, allylmetals are of particular interest due to their singular reactivity towards carbonyl compounds and to the high synthetic potential of the resulting adducts. However allylmetals have to be distinguished depending on their configurational stability.[2] While allylboranes, allylboronic esters[3] and allylsilanes[4] are configurationally stable and can be stereo-specifically transferred to a prochiral electrophile, allylzincs are prone to metallotropism and thus constitute ideal candidates to promote a dynamic kinetic resolution.[5]

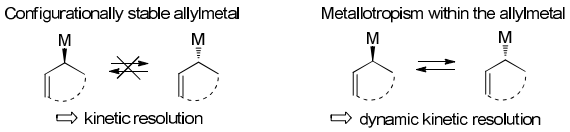

Figure 1. Classification of allylmetals.

In the boron series, enantio-enriched allylboronic esters, based on a camphor[6] or a tartaric acid[7] template, have been described. More recently, Aggarwal's group developed a highly attractive enantioselective generation of chiral boronic esters[8] which can be applied to the synthesis of enantiopure allylboronates[3b,9]. In addition to this elegant approach, catalytic enantioselective preparations of allylmetals were also reported, including, hydrosilylation,[10] hydroboration,[11] silaboration[12] of conjugated dienes and transition-metal catalyzed allylic addition[13]. Nevertheless, among the allylmetals conventionally used in organic synthesis, the chiral integrity of allylalanes has never been experienced so far.

Recently, we reported a titanium-catalyzed hydroalumination of cyclic conjugated dienes which provided allylalanes in a straightforward manner.[14] Their reaction with chiral imines occurred with low diastereoselectivity, in contrast to their allylzinc analogues for which an efficient dynamic kinetic resolution arose, affording homoallylic amines with high stereoselectivity.[15] The poor stereoselectivity observed with allylalane could reflect the absence of a dynamic resolution between both enantiomers of the organoaluminium,

If allylalanes are really configurationally stable, a kinetic resolution of the racemic mixture could be envisioned to access an enantio-enriched allylalane.[16] In this case, the discrimination of the couple of enantiomers may occur using a chiral electrophilic trap. In turn, the preserved enantiomer could next be allowed to react with a prochiral electrophile (Figure 2).

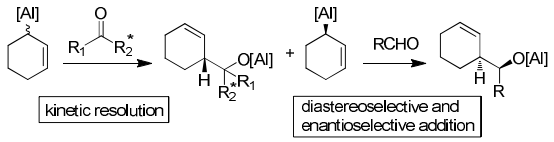

Figure 2 Towards a kinetic resolution of allylalanes

This study was initiated by identifying a carbonyl derivative able to kinetically discriminate the two enantiomers of the allylmetal. For that purpose, a series of chiral ketones was tested towards a racemic mixture of allylalane. Whereas low

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Electronic Supplementary Information (ESI) available: [^{1}H and ^{13}C NMR spectra of new compounds, HPLC copies, CCDC 1505994 (**1b-syn**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures]. See DOI: 10.1039/x0xx00000x

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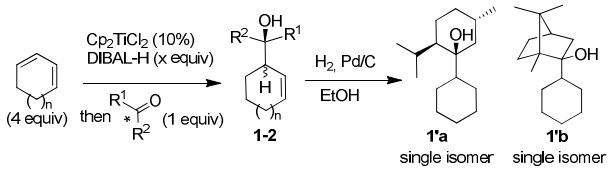
conversion was observed when using (+)-fenchone, alcohols derived from (-)-menthone and (+)-camphor were obtained quantitatively as a ca 2:1 mixture of two diastereoisomers (Table 1, entries 2 and 3). To ascertain their relative stereochemistry, **1a** and **1b** were hydrogenated (H_2, Pd/C) (Table 1) to give **1'a** and **1'b** respectively. Both were obtained as a sole isomer, indicating that the initial diastereomers are *syn* and *anti* isomers resulting from a nearly complete facial discrimination of the carbonyl group (endo addition) (Scheme 2). It was thus postulated that a divergent evolution within the couple of enantiomers of the allylmetal occured, one leading to the *syn* adduct, the other to the *anti*.

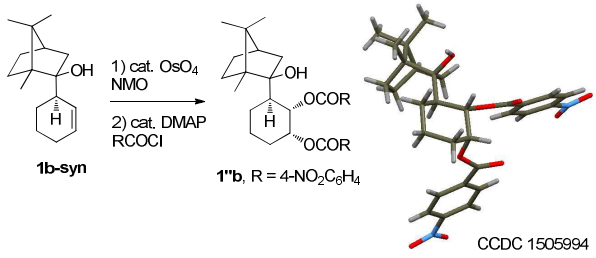
To estimate whether a kinetic resolution could also operate, additional experiments were carried out. Firstly, an excess of allylalane (3 equiv) was reacted with (+)-camphor, resulting in a remarkable increase of the selectivity (dr > 20:1, Table 1, entry 4). Secondly, the allylalane was allowed to react with *rac*-camphor. In that case, the same diastereoisomer was obtained (dr > 20:1, entry 5). The absolute configuration of the major isomer **1b-*syn***, obtained using (+)-camphor, was unambiguously assigned through X-ray diffraction studies of its derivative **1"b** (Scheme 1).

Table 1 Screening of chiral ketones



entry	n	ketone	T (°C)	equiv	**1,2** (yield, %) [a]	dr *syn*:*anti*
1	1	(+)-fenchone	rt	2	<10%	nd[b]
2	1	(-)-menthone	rt	2	**1a** (76)	1.8:1
3	1	(+)-camphor	rt	2	**1b** (62)	2:1
4	1	(+)-camphor	rt	3	**1b** (60)	20:1
5	1	(±)-camphor	rt	2	**1b** (80)	20:1
6	1	(+)-camphor	-20	2	**1b** (82)	20:1
7	1	(-)-menthone	-20	2	**1a** (69)	2.1:1
8	0	(+)-camphor	-20	3	**2b** (81)	4:1
9	0	(±)-camphor	-20	2	**2b** (71)	7.8:1

a Isolated yields. b Complex mixture of products along with starting material was obtained.



Scheme 1 Characterisation of **1b-*syn***

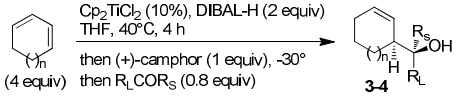
These results indicate that a chiral recognition occurred. However, a competition persists between the two enantiomeric forms of the alane at rt, unless an excess of alane is used.

Ideally, for an optimal kinetic resolution, the total consumption of one enantiomer must be ensured using two equivalents of the racemic mixture with respect to the enantiomerically pure selector. Under these conditions, It was found that at -20°C, the kinetic resolution was efficient using (+)-camphor as the chiral selector (entry 6), only one single isomer of **1b** being observable according to NMR analysis accuracy. The rate difference between the two competing reactions might be significantly high at -20°C to limit the consumption of one enantiomer. In contrast, the selectivity remained low with (-)-menthone (entry 7).

Finally, similar sequences were applied to cyclopentadiene, however lower selectivities were observed (entries 8 and 9).

The optimized conditions stated above should allow the seclusion of one single enantiomer of the allylalane in the reaction mixture. Thus, the whole sequence was tested by adding benzaldehyde at the last stage. In the case of cyclohexadiene, the corresponding homoallylalcohol was obtained with an enantiomeric excess of 87% by operating at -20°C, which was slightly enhanced at -30°C (Table 2, entries 1 and 2).

Table 2 Asymmetric allylation of aldehydes and ketones



entry	n	R_L	R_s	**3,4** (yield,%)[b]	dr[c]	er [d]
1[a]	1	Ph	H	**3a** (65)	98:2	93.5:6.5
2	1	Ph	H	**3a** (85)	98:2	94.5:5.5
3	0	Ph	H	**4a** (83)	>98:2	70:30
4[e]	0	Ph	H	**4a** (71)	>98:2	74:26
5	1	4-Br-C_6H_4	H	**3b** (89)	96:4	92:8
6	1	3,4-Cl_2-C_6H_3	H	**3c** (55)	94:6	93.5:5.5
7	1	6-Br-piperonyl	H	**3d** (82)	97:3	92:8
8	1	4-$MeCO_2$-C_6H_4	H	**3e** (75)	93:7	93:7
9	1	3-pyridyl	H	**3f** (50)	95:5	93.5:6.5
10	1	3-furyl	H	**3g** (83)	>98:2	93.5:6.5
11	1	2-indolyl	H	**3h** (64)	>98:2	93:7
12	1	(*E*)-styryl	H	**3i** (80)	>98:2	93.5:6.5
13	1	$CH(Ph)_2$	H	**3j** (58)	>98:2	90.5:9.5
14	1	TBSO-$(CH_2)_3$	H	**3k** (66)	>98:2	94.5:5.5
15	1		H	**3l** (52)	nd	dr[f] = 93:7
16[g]	1		H	**3m** (50)	nd	dr[f] = 6:94
17	1	2-Me-C_6H_4	Me	**3n** (58)	>98:2	93:7
18	1	α-tetralone		**3o** (53)	>98:2	93:7
19	1	Ph	CΞCCH$_2$OTr	**3p** (55)	88:12	93:7

[a] Carried out at -20°C. [b] Isolated yields.[c] Calculated from the crude reaction mixture. [d] Determined by HPLC on chiral phase. [e] 1.4 equiv of (+) camphor were used. [f] Could not be unambiguously determined from the crude reaction mixture, and was estimated by combining all product-containing fractions collected during the purification. [g] (-)-Camphor was used as the chiral selector.

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The same sequence was applied at -30°C to cyclopentadiene, however poor enantioselectivity was obtained (entry 3), even by employing an excess of chiral selector (entry 4), as it could be anticipated from the initial results (Table 1, entries 8 and 9).

A series of aldehydes was next tested under the better conditions (e.g. -30°C), affording homoallylic alcohols containing aromatic (entries 5-8), heteroaromatics (entries 9-11), vinylic (entry 12) or alkyl groups (entries 13 and 14) with good enantiomeric ratios (up to 94.5 : 5.5). The absolute configuration of homoallylic alcohols **3** was assigned by analogy with previously reported **3a** and **3i**.

Additionally, when enantiopure glyceraldehyde acetonide was used as the electrophile, it is noteworthy that the configuration of the newly formed stereogenic centers is subordinated to the sole configuration of the allylalane. Typically, a diastereomeric ratio of greater than 90:10 was obtained using either (+) or (-)-camphor as the chiral selector with an opposite stereoselection (entries 15 and 16), as previously reported with enantiomerically pure allyltin complexes.[17]

Finally, the methodology can also be applied to sterically dissymmetrical ketones (entries 17-19).

To rationalize the observed selectivities, several aspects should be taken in consideration. Firstly, the nucleophilic addition exclusively occurs at the endo face of (+)-camphor, irrespective of the allylalane configuration, which is in agreement with previously reported *endo*-selective allylation of camphor-derivatives.[18] The predominant formation of **1b-*syn*** is thus likely to result from the reaction of the (*S*)-enantiomer of the allylalane with (+)-camphor, and assumed to proceed through a Traxler-Zimmerman-like transition state, where the bulkier fragment of camphor is located in a *pseudo* equatorial position (Figure 3).[19] Competitively, the reaction of the (*R*)-enantiomer with (+)-camphor might produce **1b-*anti***, presumably through a different mechanistic pattern.

Secondly, the reaction involving the (*R*)-enantiomer appears to be kinetically disfavored over that of the (*S*)-enantiomer at -30°C, resulting in an efficient resolution in the case of the cyclohex-2-en-1-ylalanre.

Thirdly, once the resolution was effective, typically after 2 h at -30°C, the remaining (*R*)-enantiomer was subsequently allowed to react with the aldehyde to give the *pseudo*-enantiomer of the camphor-adduct *via* a similar chair-like transition state (Figure 3).

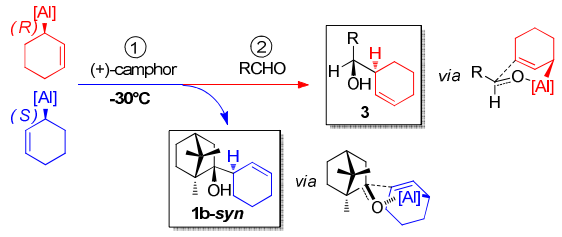
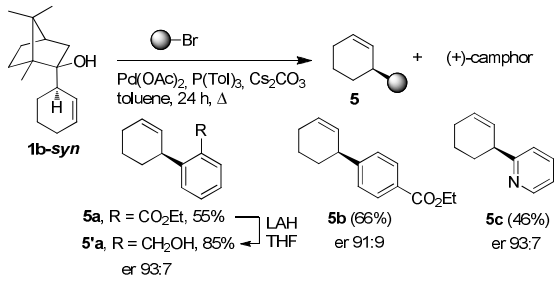


Figure 3 Mechanism Proposal

Interestingly, the procedure could be further valorized by converting the camphor-derived homoallylalcohol **1b-*syn***, side product of the resolution process. Indeed, an effective chirality transfer[20] was observed when applying the palladium-mediated retroallylation / cross-coupling reaction developed by Oshima,[21] Thus, the access to enantio-enriched 3-arylcyclohex-1-ene **5a-c** could be achieved from **1b-*syn*** by using arylbromide in the presence of $Pd(OAc)_2$, $P(Tol)_3$ and Cs_2CO_3 in toluene. Moreover, (+)-camphor was obtained as the co-product and could thus be recycled (Scheme 2).



Scheme 2. Valorisation of side product **1b-*syn***

In summary, an efficient kinetic resolution of the two enantiomers of cyclic allylalanes using readily available (+)-camphor as the chiral selector is described. This approach enables to *in-situ* provide the alane in the enantiomerically enriched form, which diastereoselectively reacts with carbonyl compounds, affording homoallylalcohols with enantiomeric ratios up to 94.5 : 5.5. In parallel, the cyclohex-3-enylisoborneol, generated during the resolution step, could be converted into 3-arylcyclohexenes with er up to 93 : 7. Optimization of the chiral selector structure and generalization of the method to others allylalanes are currently under investigations.

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Notes and references

1 For recent examples of enantioselective C-Si bond-forming reactions see: (a) E. Hartmann and M. Oestreich, *Angew. Chem., Int. Ed.,* 2010, **49**, 6195; (b) E. Hartmann and M. Oestreich, *Org. Lett.,* 2012, **14**, 2406; (c) K.-s. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.,* 2010, **132**, 2898; (d) I. Ibrahem, S. Santoro, F. Himo and A. Córdova, *Adv. Synth. Catal.,* 2011, **353**, 245; (e) V. Pace, J. P. Rae, H. Y. Harb and D. J. Procter, *Chem. Commun.,* 2013, **49**, 5150; (f) J. Plotzitzka and C. Kleeberg, *Organometallics,* 2014, **33**, 6915; for recent examples of enantioselective C-B bond forming reactions see: (g) J. M. O'Brien, K.-s. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.,* 2010, **132**, 10630; (h) R. Corberán, N. W. Mszar and A. H. Hoveyda, *Angew. Chem., Int. Ed.,* 2011, **50**, 7079; (i) F. Meng, H. Jang and A. H. Hoveyda, *Chem.-Eur. J.,* 2013, **19**, 3204; (j) N. Matsuda, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.,* 2013, **135**, 4934; (k) H. Jang, B. Jung and A. H. Hoveyda, *Org. Lett.,* 2014, **16**, 4658; for examples of

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DOI: 10.1039/C6CC08649G

enantioselective C-Sn bond formation reaction see : (l) T. Jia, P. Cao, D. Wang, Y. Lou and J. Liao, *Chem.-Eur. J.,* 2015, **21**, 4918; (m) M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.,* 2004, **126**, 3688.

2 Y. Yamamoto and N. Asao, *Chem. Rev*., 1993, **93**, 2207.

3 (a) F. Peng and D.G. Hall, *J. Am. Chem. Soc*., 2007, **129**, 3070; (b) J. L.-Y. Chen, H. K. Scott, M. J. Hesse, C. L. Willis and V. K. Aggarwal, *J. Am. Chem. Soc.,* 2013, **135**, 5316; (c) H. Ito, S. Kunii and M. Sawamura, *Nature Chem*., 2010, **2**, 972.

4 (a) D. Li, T. Tanaka, H. Ohmiya and M. Sawamura, *Org. Lett*., 2010, **12**, 3344; (b) Y. Yoshimura, M. Ohta, T. Imahori, T. Imamichi and H. Takahata, *Org. Lett.,* 2008, **16**, 3449; (c) H. S. Park, J. Wook Han, R. Shintani and T. Hayashi, *Tetrahedron : Asymmetry,* 2013, **24**, 418; (d) J. Wook Han and T. Hayashi, *Tetrahedron : Asymmetry,* 2002, **13***,* 325; (e) J.-M. Adam, L. de Fays, M. Laguerre and L. Ghosez, *Tetrahedron,* 2004, **60**, 7325.

5 (a) J. Bejjani, C. Botuha, F. Chemla, F. Ferreira, S. Magnus and A. Perez-Luna, *Organometallics,* 2012, **31**, 4876; (b) C. J. Cordier, R. J. Lundgren and G. C. Fu, *J. Am. Chem. Soc*., 2013, **135**, 10946; (c) N. P. Mulholland, G. Pattenden and I. A. S. Walters, *Org. Biomol. Chem., 2008,* **6**, 2782; (d) T. Ling, V. R. Macherla, R. R. Manam, K. A. Mc Arthur and B. C. M. Potts, *Org. Lett*., 2007, **9**, 2289; (e) L. R. Reddy, B. Hu, M. Prashad and K. Prasad, *Org. Lett*., 2008, **10**, 3109.

6 (a) F. R. Struth and C. H Hirschhäuser, *Eur. J. Org. Chem*., 2016, 958; (b) M. Chen and W. R. Roush, *Org. Lett*., 2010, **12**, 2706.

7 J. Pietruszka, N. Schöne, W. Frey and L. Grundl, *Chem.-Eur. J.,* 2008, **14**, 5178.

8 (a) J. L. Stymiest, V. Bagutski, R. M. French and V.K. Aggarwal, *Nature,* 2008, **456**, 778; (b) V. Bagutski, R. M. French and V. K. Aggarwal, *Angew. Chem., Int., Ed.* 2010, **49**, 5142; (c) D. Leonori and V. K. Aggarwal, *Acc. Chem. Res*., 2014, **47**, 3174; (d) S. Balieu, G. E. Hallett, M. Burns, T. Bootwicha, J. Studley and V. K. Aggarwal, *J. Am. Chem. Soc*., 2015, **137**, 4398; e) S. Roesner, D. J. Blair and V. K. Aggarwal, *Chem. Sci*., 2015, **6**, 3718.

9 (a) R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott and V. K. Aggarwal, *Angew. Chem., Int. Ed.,* 2011**, 50**, 3760; (b) P. J. Unworth, D. Leonori and V. K. Aggarwal, *Angew. Chem., Int. Ed.,* 2014, **53**, 9846; (c) J. L.-Y. Chen and V. K. Aggarwal, *Angew. Chem., Int. Ed.* 2014, **53**, 10992; (d) M. Althaus, A. Mahmood, J. R. Suárez, S. P. Thomas and V. K. Aggarwal, *J. Am. Chem. Soc*., 2010, **132**, 4025.

10 a) K.-s. Lee, H. Wu, F. Haeffner and A. H. Hoveyda, *Organometallics,* 2012, **31**, 7823; b) J. W. Han and T. Hayashi, *Tetrahedron*: *Asymmetry,* 2010, **21**, 2193; c) J. W. Han, N. Tokunaga and T. Hayashi, *Helv. Chem. Acta,* 2002, **85**, 3848; d) T. Hayashi, K. Kabeta, T. Yamamoto, K. Tamao and M. Kumada, *Tetrahedron Lett.,* 1983, **24**, 5661; e) T. Hayashi, J. W. Han, A. Takeda, J. Tang, K. Nohmi, K. Mukaide, H. Tsuji and Y. Uozumi, *Adv. Synth. Catal.,* 2001, **343**, 279.

11 (a) H. C. Brown, K. S. Bhat and P. K. Jadhav, *J. Am. Chem. Soc.,* 1985, **107**, 2564; (b) H. C. Brown, K. S. Bhat and P. K. Jadhav, *J. Chem. Soc., Perkin Trans. I,* 1991, 2633; (c) Y. Sasaki, C. Zhong, M. Sawamura and H. Ito, *J. Am. Chem. Soc.,* 2010, **132**, 1226; (d) E. González, L. Muñoz-Hernández, E. Alicea, B. Singaram, G. W. Kabalka and J. A. Soderquist, *Org. Lett*., 2015, **17**, 4368.

12 (a) M. Gerdin and C. Moberg, *Adv. Synth. Catal.,* 2005, **347**, 749; (b) M. Gerdin, M. Penhoat, R. Zalubovskis, C. Pétermann and C. Moberg, *J. Organomet. Chem.,* 2008, **693**, 3519.

13 (a) L. Carosi and D. G. Hall, *Angew. Chem., Int., Ed.* 2007, **46**, 5913; (b) Y. Lee and A. H. Hoveyda *J. Am. Chem. Soc.,* 2009, **131**, 3160; (c) J. K. Park and D. T. McQuade, *Synthesis,* 2012, 1485; (d) M. A. Kacprzynski, T. L. May, S. A. Kazane and A. H. Hoveyda, *Angew. Chem., Int. Ed.,* 2007, **46**, 4554; (e) M. Takeda, R. Shintani and T. Hayashi, *J. Org. Chem.,* 2013, **78**, 5007; (f) L. B. Delvos, D. J. Vyas and M. Oestreich, *Angew. Chem., Int. Ed.,* 2013, **52**, 4650.

14 J. Joseph, F. Jaroschik, K. V. Radhakrishnan, D. Harakat, J.-L. Vasse and J. Szymoniak, *Chem.-Eur. J.,* 2014, **20**, 5433.

15 M. Coffinet, S. Lamy, F. Jaroschik and J.-L. Vasse, *Org. Biomol. Chem.,* 2016*,* **14**, 69.

16 The access to enantio-enriched allyltin derivatives by kinetic resolution was previously reported by reacting a racemic mixture of allytin with enantiopure cyclohexylidene glyceraldehyde: F. Fliegel, I. Beaudet and J.-P. Quintard, *J. Organometallic Chem*., 2001, **624**, 383.

17 (a) J. A. Marshall, *Chem. Rev*., 1996, **96**, 31; (b) J. A. Marshall, *J. Org. Chem*., 2007, **72**, 8153.

18 (a) B. Schmidt and L. Staude, *J. Organomet. Chem*., 2006, **691**, 5218; (b) D. J. Dixon, R. A. J. Horan and N. J. T. Monck, *Org. Lett*., 2004, **6**, 4423; (c) S. Sezer, Y. Gümrükçü, E. Sahin and C. Tanyeli, *Tetrahedron*: *Asymmetry,* 2008, **19**, 2705; (d) C.-L. K. Lee, C.-H. A. Lee, K.-T. Tan and T.-P. Loh, *Org. Lett*., 2004, **6**, 1281; (e) W. H. Bunnelle, M. A. Rafferty and S. L. Hodges, *J. Org. Chem*., 1987, **52**, 1603.

19 (a) Z. Peng, T. D. Blümke, P. Mayer and P. Knochel, *Angew. Chem., Int. Ed.,* 2010, **49**, 8516-8519; (b) H. Ren, G. Dunet, P. Mayer and P. Knochel, *J. Am. Chem. Soc.,* 2007, **129**, 5376..

20 R.Wakabayashi, D. Fujino, S. Hayashi, H. Yorimitsu and K. Oshima, *J. Org. Chem*., 2010, **75**, 4337.

21 (a) S. Hayashi, K. Hirano, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.,* 2006, **128**, 2210; (b) M. Iwasaki, S. Hayashi, K. Hirano, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc*., 2007, **129**, 4463; (c) S. Hayashi, K. Hirano, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.,* 2007, **129**, 12650.

