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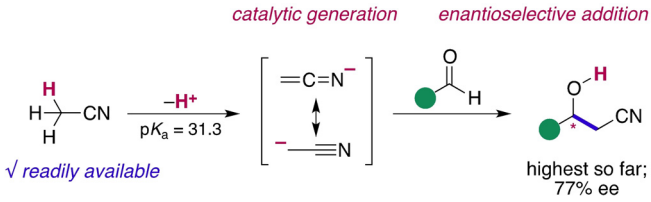
Homogeneous Catalysis

Direct Catalytic Asymmetric Addition of Alkylnitriles to Aldehydes with Designed Nickel–Carbene Complexes

Akira Saito, Shinya Adachi, Naoya Kumagai, and Masakatsu Shibasaki**

Abstract: *A direct catalytic asymmetric addition of acetonitrile to aldehydes that realizes over 90 % ee is the ultimate challenge in alkylnitrile addition chemistry. Herein, we report achieving high enantioselectivity by the strategic use of a sterically demanding Ni^{II} pincer carbene complex, which afforded highly enantioenriched β-hydroxynitriles. This highly atom-economical process paves the way for exploiting inexpensive acetonitrile as a promising C2 building block in a practical synthetic toolbox for asymmetric catalysis.*

Catalytic asymmetric addition reactions of anionic carbon nucleophiles are critical in organic synthesis for constructing highly complex enantioenriched molecular architectures. Despite the widespread application of enolates as common active nucleophiles for this purpose, chemists have paid little attention to α-cyanocarbanions because of their limited accessibility. Nitriles, direct precursors of α-cyanocarbanions, are generally stable and regarded as solvents for chromatography and various reactions owing to their inert nature toward a wide range of chemical transformations.[1] Acetonitrile is the most widely used nitrile-based common solvent, but has little utility as a carbon pronucleophile in catalytic asymmetric reactions because 1) its high pK_a (31.3 in DMSO) significantly interferes with catalytic generation of the corresponding α-cyanocarbanion,[2–7] and 2) the minimal steric bias of the α-cyanocarbanion significantly raises the hurdle for decent stereocontrol at the stage of carbon-carbon bond formation with certain electrophiles (Scheme 1). Although recent advances in catalysis with well-designed metal complexes allow for catalytic promotion of direct addition of acetonitrile to various electrophiles,[8] the issue of stereocontrol is more serious and has only been partly addressed.[9,10] Our group recently reported a highly enantioselective (average 95 % *ee*) acetonitrile addition to sterically biased *N*-diphenylphosphinoyl (*N*-Dpp) imines[11] with a specific Ni^{II} complex having a deep vaulted architecture.[9h] Direct addition of acetonitrile to aldehydes providing β-hydroxynitriles, however, remained a challenge and the enantioselectivity was only moderate (up to 77 % *ee*).[9b] Herein, we disclose the catalytic conditions that directly produce β-hydroxynitriles from aldehydes and alkylnitriles with the highest enantioselectivity yet reported. While the enantioselectivity is sensitive to the aldehyde structure, this achievement is an important step toward the prospective development of general catalytic asymmetric conditions for alkylnitrile addition reactions.



Scheme 1. Catalytic asymmetric addition of acetonitrile to aldehydes.

We began our study by evaluating the previously identified Ni^{II} carbene complex capable of highly enantioselective addition of acetonitrile to *N*-Dpp imines.[9h] The reaction of acetonitrile with 2-naphthaldehyde **1a** under the previously determined optimal conditions from the reaction with *N*-Dpp imines using Ni^{II} pincer complex **C1** unexpectedly afforded the corresponding product **2a** with only 63 % *ee* (Table 1, entry 1).[12,13] Tracing the enantiopurity of **2a** in the course of the reaction at room temperature revealed the gradual erosion of enantiopurity, indicating that a retro reaction occurred (Figure 1). We next examined the effects of a co-solvent system with alcoholic solvents to suppress the undesired retro reaction. While MeOH halted the catalysis and *t*BuOH was barely impactful, a CH_3CN/*i*PrOH mixed solvent system improved the enantioselectivity of **2a** to 76 % *ee* (entries 2–4). Lowering the reaction temperature further improved the enantioselectivity to 93 % *ee* (entry 5). Under these satisfactory conditions, we systematically investigated the substituent effect of the Ni^{II} pincer complex (entries 6–12). Complexes **C2–4** armed with alkyl substituents (*i*Pr, *t*Bu, Bn) were generally ineffective and delivered product **2a** in low to modest yield and enantioselectivity (entries 6–8). Anticipating more sterically biasing Ni complexes with aromatic substituents, methylated benzenes and naphthyl units were tested (entries 9–12). Unexpectedly, complex **C5** with a larger mesityl substituent afforded only trace amounts of **2a** with lower enantioselectivity (77 % *ee*), presumably due to excessive steric bias (entry 9). Complex **C6** bearing a modestly biasing unit of 3,5-xylyl groups produced **2a** with 94 % *ee* (entry 10). Although complex **C7** with 1-naphthyl groups provided a narrower pocket en route to the Ni^{II} center than complex **C8** with 2-naphthyl groups, the resulting enantioselectivity was only slightly inferior, and **C8** produced enantioselectivity similar to that of **C1** and **C6** (entries 11, 12). Based on the yield and broad availability of the ligand skeleton (from (*R*)-phenylglycine), the conditions of entry 5

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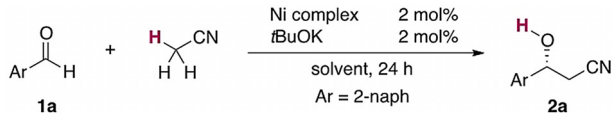
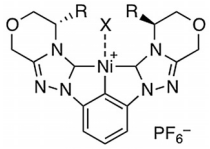
Table 1: Optimization of direct catalytic addition of acetonitrile to 2-naphthaldehyde **1a**.[a]



Entry	Ni complex	R	Solvent[b]	*T* [°C]	Yield [%]	*ee* [%]
1	**C1**	Ph	CH_3CN	0	88	63
2	**C1**	Ph	CH_3CN/MeOH	0	–	–
3	**C1**	Ph	CH_3CN/*i*PrOH	0	91	76
4	**C1**	Ph	CH_3CN/*t*BuOH	0	92	64
5	**C1**	Ph	CH_3CN/*i*PrOH	−20	>99	93
6	**C2**[c]	*i*Pr	CH_3CN/*i*PrOH	−20	63	45
7	**C3**[c]	*t*Bu	CH_3CN/*i*PrOH	−20	23	48
8	**C4**[c]	Bn	CH_3CN/*i*PrOH	−20	5	44
9	**C5**	mesityl	CH_3CN/*i*PrOH	−20	5	77
10	**C6**	3,5-xylyl	CH_3CN/*i*PrOH	−20	83	94
11	**C7**	1-naph	CH_3CN/*i*PrOH	−20	88	87
12	**C8**	2-naph	CH_3CN/*i*PrOH	−20	87	92



C1: R = Ph
C2: R = *i*Pr
C3: R = *t*Bu
C4: R = Bn
(X = $NCCH_3$)

C5: R = mesityl
C6: *R* = 3,5-xylyl
C7: *R* = 1-naph
C8: *R* = 2-naph

[a] **1a**: 0.1 mmol, 0.1 M on **1a**. [b] For mixed solvent conditions, a 1/1 (v/v) ratio of solvents was used. [c] The catalyst was prepared from Ni-Cl complex and $AgPF_6$, which was directly used without isolation.

using complex **C1** were considered optimal for further study. It should be noted that the present catalysis was capable to promote the direct addition of propionitrile to **1a** to give *anti*-**3a** as a major diastereomer with high enantioselectivity (Scheme 2), albeit the diastereoselectivity needs further improvement.

The proposed catalytic cycle is delineated in Figure 2a. On the basis of the detailed DFT study reported by Ariafard et al.,[8l] *N*-bound cyanocarbanion/**C1** complex **I** formed from **C1** and *t*BuOK, which is in equilibrium with *C*-bound complex **II**, is a plausible intermediate en route to the enantioselective addition to aldehyde **1**. To gain insight into the effectiveness of complex **C1**, a steric map of the catalytic pocket was generated with the SambVca 2.1 Web tool based on the crystal structure of Cl salt of **C1** (Figure 2).[14,15] The buried volume of 57.4% indicates a highly congested environment around the Ni^{II} center, which is geometrically visualized with altimetric contour levels

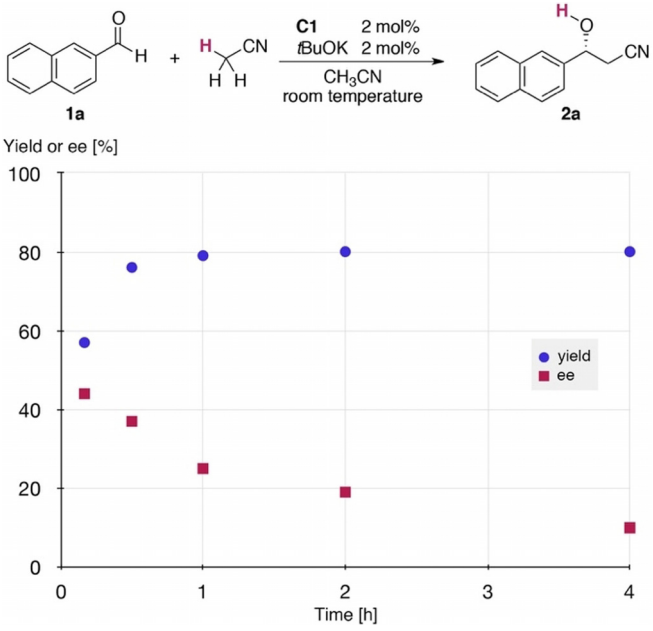
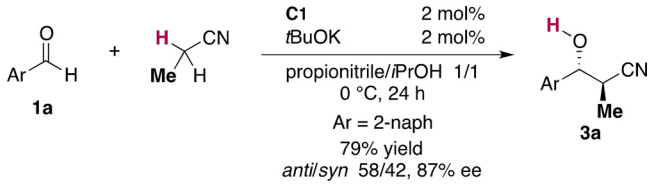


Figure 1. Time course of the reaction of naphthaldehyde **1a** and acetonitrile at room temperature.



Scheme 2. Catalytic asymmetric addition of propionitrile to 2-naphthaldehyde **1a**.

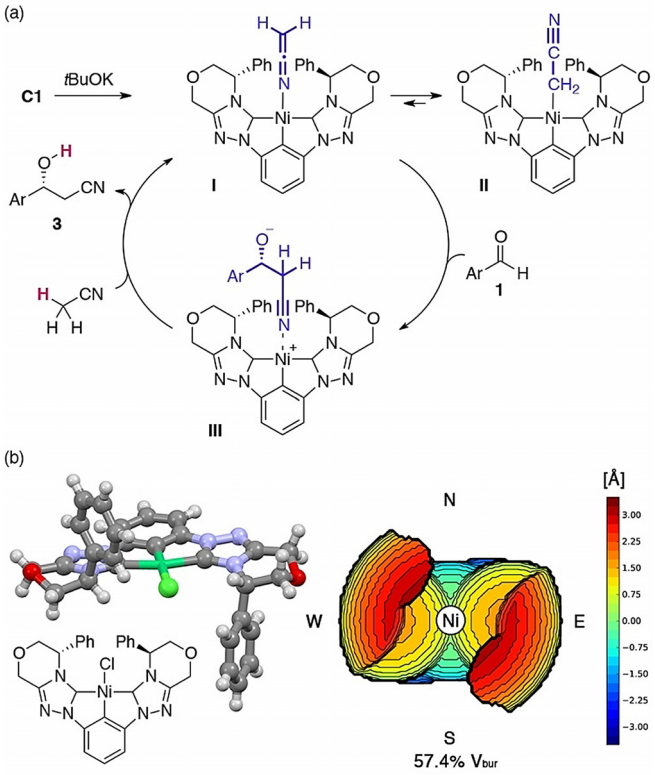


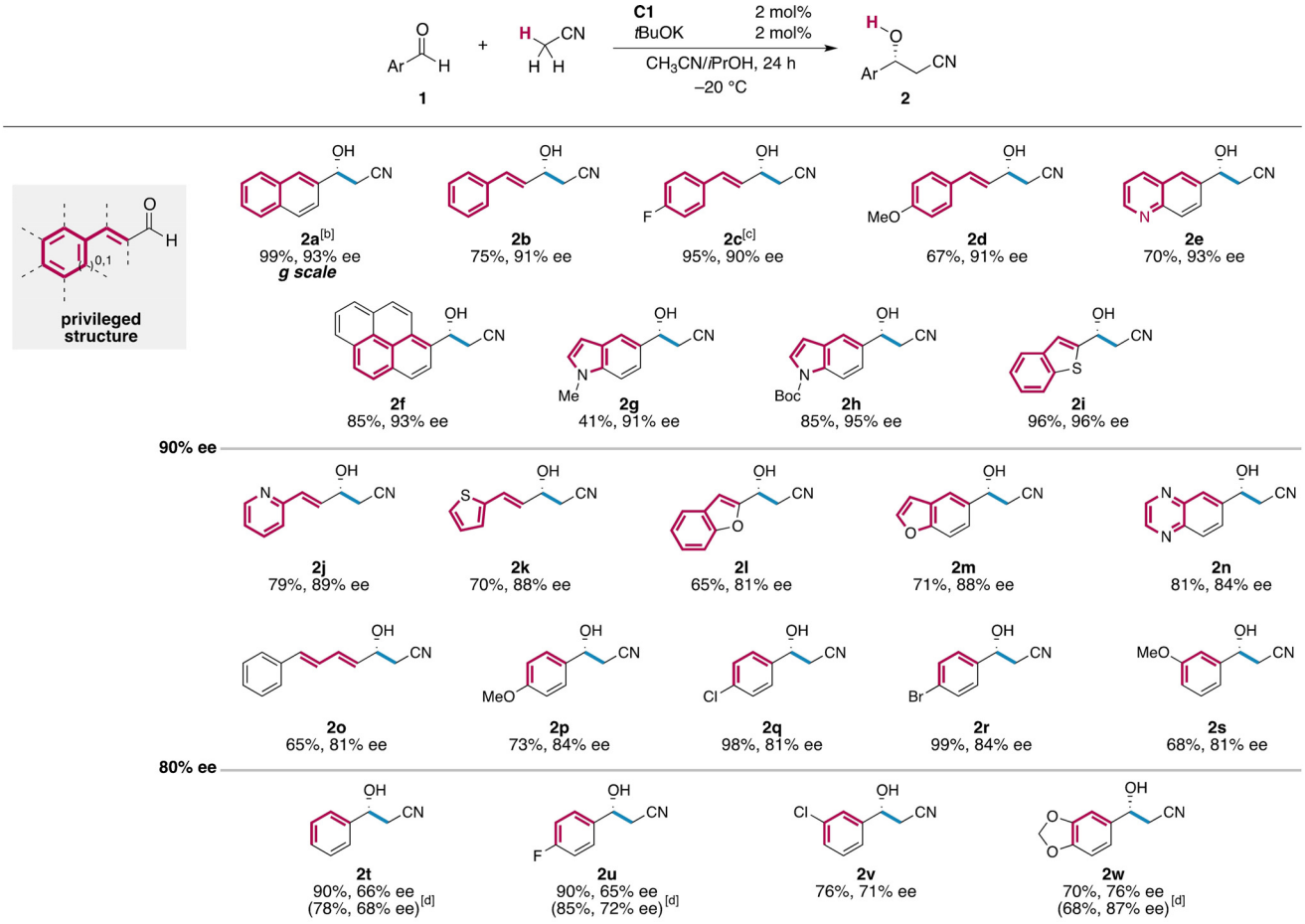
Figure 2. a) Proposed catalytic cycle. b) X-ray crystal structure of Cl salt of **C1**, buried volume, and corresponding steric map. Bondi radii scaled by 1.17, sphere radius 3.5 Å, and mesh spacing 0.1 Å.

deviated from the horizontal plane containing the Ni center. The steric bias is mainly located in the northwestern and southeastern quadrants, while northeastern and southwestern trajectories are opened to achieve high enantioselectivity. The thus-formed zwitterionic intermediate **III** is likely responsible for deprotonation of acetonitrile to drive the following catalytic cycle.

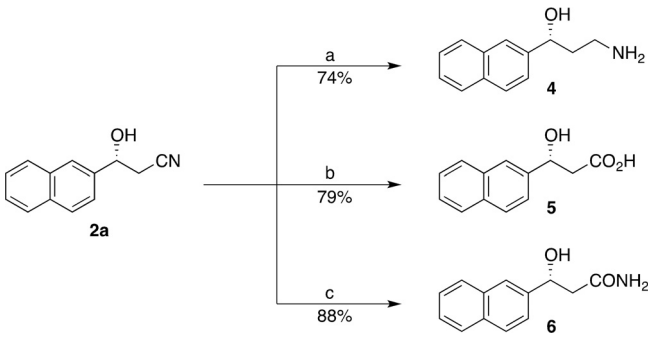
With the optimal conditions in hand, the substrate scope was systematically studied as summarized in Table 2.[16,17] The present catalysis is scalable and the reaction of **1a** was performed on a one-gram scale without any detrimental effects. Intriguingly, enantioselectivity is highly sensitive to the aldehyde structure, revealing that the styryl unit is privileged to reach >90% *ee*. Other than naphthaldehyde **1a**, (*E*)-cinnamaldehyde **1b** was suitable for the present catalytic conditions to give **2b** in 91% *ee*, albeit with somewhat eroded yield. *para*-Substituents barely interfered with the enantioselectivity, irrespective of their electron-withdrawing or -donating nature (**2c**,**d**). Quinoline-5-carboxaldehyde **1e**, sharing the privileged unit, gave the corresponding product **2e** in 93% *ee*, demonstrating that a Lewis basic functionality located far from the carbonyl moiety is tolerated. π-Extended aldehyde **1f** with a pyrene unit was also accommodated, resulting in high enantioselectivity (93% *ee*). Aldehydes with an indole unit are structurally similar to the privileged styryl unit and afforded the products **2g** and **2h** with high enantioselectivity, while the *N*-Me derivative **1g** produced a low yield, likely due to lower electrophilicity. The thiophene architecture was recognized as a privileged structure and product **2i** was isolated with the highest enantioselectivity (96% *ee*). A different heteroatom substitution pattern on the privileged structural unit led to a marginal loss in enantioselectivity (below 90% *ee*) (**2j–n**). Embedding an ethylene unit into the privileged structure resulted in eroded enantioselectivity (aldehyde **1b** vs. **1o**), indicating the pivotal role of the styryl unit to assure enantiodifferentiation. The reduced enantioselectivity observed for benzaldehyde derivatives further supported this trend; while *p*-MeO, -Cl, -Br, or *m*-MeO substituted aldehydes **1p–s** exhibited no less than 80% *ee*, *p*-F or *m*-Cl derivatives **1u,v** as well as benzaldehyde **1t** gave the corresponding products with less satisfactory enantioselectivity. Bulkier catalyst **C6** partly improved the enantioselectivity of **1t** and **1u**, and stereodifferentiation of sterically larger piperonal **1w** was more significantly enhanced to 87% *ee*.

The cyano groups of the product can be treated as masked amine and carboxyl functionalities (Scheme 3). 1,3-Amino alcohol **4** was generated by treatment with $BH_3{\cdot}SMe_2$ in

Table 2: Substrate scope of direct catalytic asymmetric addition of acetonitrile to aldehydes.[a]



[a] **1**: 0.1 mmol, 0.1 M on **1**. [b] 1.0 g of **1a** was used. [c] 5 mol% of **C1** and *t*BuOK were used. [d] **C6** instead of **C1** was used as catalyst.



Scheme 3. Transformation of the product. a) $BH_3{\cdot}SMe_2$, THF, reflux, 36 h; b) 3 M NaOH aq., 30% H_2O_2 aq., 60 °C, 72 h; c) Na_2CO_3, 30% H_2O_2 aq., acetone, rt, 16 h.

refluxing THF. This is complimentary to the nitroaldol reaction using nitroalkanes as nucleophiles, providing 1,2-amino alcohol upon reduction of nitro group. Conversion to carboxylic acids **5** and primary amides **6**, having the same oxidation level as the cyano group, was selectively accomplished by hydrolysis with H_2O_2 aq. with simple attenuation of the basicity and reaction temperature.

In conclusion, we developed a highly enantioselective direct catalytic addition of acetonitrile to aldehydes. Although the enantioselectivity is sensitive to the structural features of the aldehydes used, the strategic use of a Ni^{II}–pincer complex with a deep vaulted catalytic pocket accomplished the highest enantioselectivity yet reported for common aromatic aldehydes. We believe that this achievement is an important step toward the development of a general catalytic asymmetric toolbox to exploit acetonitrile as a common C2 building block in organic synthesis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehydes · enantioselectivity · homogeneous catalysis · nickel · nitriles

[1] a) J. G. Vercade, P. B. Kisanga, *Aldrichimica Acta* **2004**, *37*, 3–14; b) R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2015**, *54*, 13170–13184; *Angew. Chem.* **2015**, *127*, 13366–13380.
[2] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.
[3] R. Peters, S. Jautze, *Synthesis* **2009**, 365–388.
[4] a) M. B. Cid, S. Duce, S. Morales, E. Rodrigo, J. L. Ruano, *Org. Lett.* **2010**, *12*, 3586–3589; b) R. Yazaki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 5522–5531; c) K. Hyodo, S. Nakamura, K. Tsuji, T. Ogawa, Y. Funahashi, N. Shibata, *Adv. Synth. Catal.* **2011**, *353*, 3385–3390; d) Y. Yanagida, R. Yazaki, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2011**, *50*, 7910–7914; *Angew. Chem.* **2011**, *123*, 8056–8060; e) M. Kondo, M. Omori, T. Hatanaka, Y. Funahashi, S. Nakamura, *Angew. Chem. Int. Ed.* **2017**, *56*, 8677–8680; *Angew. Chem.* **2017**, *129*, 8803–8806.
[5] a) M. Kondo, M. Sugimoto, S. Nakamura, *Chem. Commun.* **2016**, *52*, 13604–13607; b) P. V. Balaji, L. Brewitz, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2019**, *58*, 2644–2648; *Angew. Chem.* **2019**, *131*, 2670–2674; c) R. Ding, Z. A. De Los Santos, C. Wolf, *ACS Catal.* **2019**, *9*, 2169–2176; d) P. V. Balaji, Z. Li, A. Saito, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2020**, *26*, 15524–15527.
[6] a) M. Kondo, N. Kobayashi, T. Hatanaka, Y. Funahashi, S. Nakamura, *Chem. Eur. J.* **2015**, *21*, 9066–9070; b) M. Kondo, H. Saito, S. Nakamura, *Chem. Commun.* **2017**, *53*, 6776–6779; c) S. Nakamura, A. Tokunaga, H. Saito, M. Kondo, *Chem. Commun.* **2019**, *55*, 5391–5394.
[7] a) T. Arai, I. Oka, T. Morihata, A. Awata, H. Masu, *Chem. Eur. J.* **2013**, *19*, 1554–1557; b) X. Chen, H. Chen, X. Ji, H. Jiang, Z. J. Yao, H. Liu, *Org. Lett.* **2013**, *15*, 1846–1849; c) S. Kuwano, T. Suzuki, Y. Hosaka, T. Arai, *Chem. Commun.* **2018**, *54*, 3847–3850; d) T. Arai, A. Nakamura, *Synlett* **2019**, *30*, 1356–1360.
[8] a) B. A. D'Sa, P. Kisanga, J. G. Verkade, *J. Org. Chem.* **1998**, *63*, 3961–3967; b) P. Kisanga, D. McLeod, B. D'Sa, J. Verkade, *J. Org. Chem.* **1999**, *64*, 3090–3094; c) P. B. Kisanga, J. G. Verkade, *J. Org. Chem.* **2000**, *65*, 5431–5432; d) J. G. Verkade, P. B. Kisanga, *Tetrahedron* **2003**, *59*, 7819–7858; e) N. Kumagai, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 13632–13633; f) L. Fan, O. V. Ozerov, *Chem. Commun.* **2005**, 4450–4452; g) N. Kumagai, S. Matsunaga, M. Shibasaki, *Chem. Commun.* **2005**, 3600–3602; h) N. Kumagai, S. Matsunaga, M. Shibasaki, *Tetrahedron* **2007**, *63*, 8598–8608; i) A. Goto, K. Endo, Y. Ukai, S. Irle, S. Saito, *Chem. Commun.* **2008**, 2212–2214; j) A. Goto, H. Naka, R. Noyori, S. Saito, *Chem. Asian J.* **2011**, *6*, 1740–1743; k) S. Chakraborty, Y. J. Patel, J. A. Krause, H. Guan, *Angew. Chem. Int. Ed.* **2013**, *52*, 7523–7526; *Angew. Chem.* **2013**, *125*, 7671–7674; l) A. Ariafard, H. Ghari, Y. Khaledi, A. Hossein Bagi, T. S. Wierenga, M. G. Gardiner, A. J. Canty, *ACS Catal.* **2016**, *6*, 60–68.
[9] a) Y. Suto, N. Kumagai, S. Matsunaga, M. Kanai, M. Shibasaki, *Org. Lett.* **2003**, *5*, 3147–3150; b) Y. Suto, R. Tsuji, M. Kanai, M. Shibasaki, *Org. Lett.* **2005**, *7*, 3757–3760; c) Y. Kawato, N. Kumagai, M. Shibasaki, *Chem. Commun.* **2013**, *49*, 11227–11229; d) T. Deng, H. Wang, C. Cai, *Eur. J. Org. Chem.* **2014**, 7259–7264; e) D. Sureshkumar, V. Ganesh, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2014**, *20*, 15723–15726; f) Y. Yamashita, I. Sato, H. Suzuki, S. Kobayashi, *Chem. Asian J.* **2015**, *10*, 2143–2146; g) S. Lin, N. Kumagai, M. Shibasaki, *Org. Biomol. Chem.* **2016**, *14*, 9725–9730; h) A. Saito, N. Kumagai, M. Shibasaki, *Org. Lett.* **2019**, *21*, 8187–8190.
[10] S. E. Denmark, T. W. Wilson, M. T. Burk, J. R. Heemstra, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 14864–14865.
[11] S. M. Weinreb, R. K. Orr, *Synthesis* **2005**, 1205–1227.
[12] Y. Ma, S. Wei, J. Wu, F. Yang, B. Liu, J. Lan, S. Yang, J. You, *Adv. Synth. Catal.* **2008**, *350*, 2645–2651.
[13] S. Wei, X. Li, Z. Yang, J. Lan, G. Gao, Y. Xue, J. You, *Chem. Sci.* **2012**, *3*, 359–363.
[14] a) A. Poater, F. Ragone, R. Mariz, R. Dorta, L. Cavallo, *Chem. Eur. J.* **2010**, *16*, 14348–14353; b) L. Falivene, R. Credendino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano, L. Cavallo, *Organometallics* **2016**, *35*, 2286–2293; c) L. Falivene, Z. Cao, A.

Petta, L. Serra, A. Poater, R. Oliva, V. Scarano, L. Cavallo, *Nat. Chem.* **2019**, *11*, 872 – 879.
[15] The crystallographic data is associated with Ref. [8h].
[16] The reaction using aliphatic aldehyde needs further development: the reaction of acetonitrile and cyclohexanecarboxaldehyde gave the corresponding product in 14% yield (potassium salt of BHT was used instead of *t*BuOK, rt, 24 h).
[17] The reaction using ketone needs to be further development: methyl benzoylformate gave the corresponding product in 45% yield and 45% *ee* (w/o *i*PrOH, 0 °C, 24 h).

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