Article

anti-Selective Catalytic Asymmetric Nitroaldol Reaction of #-Keto Esters; Intriguing Solvent Effect, Flow Reaction, and Synthesis of APIs

Tomoya Karasawa, Raphaël Oriez, Naoya Kumagai, and Masakatsu Shibasaki

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b08236 • Publication Date (Web): 03 Sep 2018

anti-Selective Catalytic Asymmetric Nitroaldol Reaction of α-Keto Esters; Intriguing Solvent Effect, Flow Reaction, and Synthesis of APIs

Tomoya Karasawa, Raphaël Oriez, Naoya Kumagai,* and Masakatsu Shibasaki*

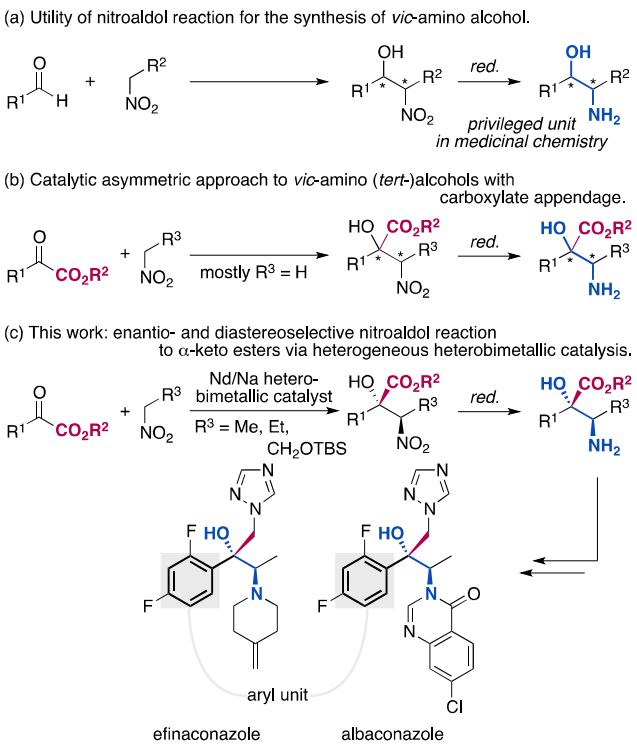
Institute of Microbial Chemistry (BIKAKEN), 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan.

ABSTRACT: A rare-earth metal/alkali metal bimetallic catalyst proved particularly effective for enantioselectively coupling nitroalkanes and α-keto esters in an *anti*-selective manner to afford synthetically versatile, densely functionalized, and optically active α-nitro tertiary alcohols. A chiral diamide ligand captured two distinct metal cations, giving rise to a catalytically competent solid-phase heterobimetallic catalyst by simple mixing via self-assembly. The advantage of the solid-phase asymmetric catalyst was realized by successful application to the enantio- and diastereoselective reaction in a continuous-flow platform. The use of closely-related solvents in terms of structures and polarity parameters, THF and its methylated congener 2-Me-THF, had an unexpectedly large solvent effect both on the reaction rate and the stereoselectivity. The nitroaldol products share a privileged unit for active pharmaceutical ingredients (APIs), as demonstrated by the streamlined enantioselective synthesis of the marketed antifungal agents efinaconazole and albaconazole.

INTRODUCTION

The concept of sustainability has gained increasing popularity in developing practical synthetic reactions for application to production processes. The nitroaldol reaction is particularly advantageous in this regard (Scheme 1a), because 1) substrates are readily available; 2) the reaction forges a C–C bond to construct the main skeleton of the molecule of interest; 3) the reaction installs consecutive hydroxyl and nitro groups on stereogenic carbons; and 4) the reaction generally proceeds under proton transfer conditions by the actions of a catalyst with perfect atom economy.[1,2] Hence, the sheer number of developments utilizing the catalytic asymmetric nitroaldol reaction to stereoselectively couple aldehydes and nitroalkanes[3,4] reported since its first disclosure in 1992 is not surprising.[5] A decade of intense research revealed that this method is valid for α-keto esters as electrophiles to access *vic*-amino alcohols including the *tert*-alcohol substructure with an additional carboxylate group,[6] expanding the opportunity to meet the increasing demand for densely functionalized synthons (Scheme 1b). This catalyst-driven process is highly useful in terms of atom economy, but the application of a higher nitroalkane than nitromethane in this catalytic process has remained elusive, and the introduction of an R^3 substituent with decent stereocontrol of an additional stereogenic center has remained problematic. Indeed, in contrast to the extensive literature coverage of the reaction of nitromethane to α-keto esters,[6-7] there are only two reports of the diastereo- and enantioselective variant. Nagasawa et al.[8] and Ooi et al.[9,10] independently documented complementary *syn*- and *anti*-selective reactions using aliphatic α-keto esters, but aromatic substrates were less tractable.[11] Given that arylated *vic*-amino (*tert*-) alcohols are privileged in marketed antifungal agents, we were particularly interested in applying our rare earth metal (RE)/alkali metal heterobimetallic catalyst[12] to incorporate

Scheme 1. Nitroaldol Reaction as a Powerful Tool for the Synthesis of *vic*-Amino Alcohols



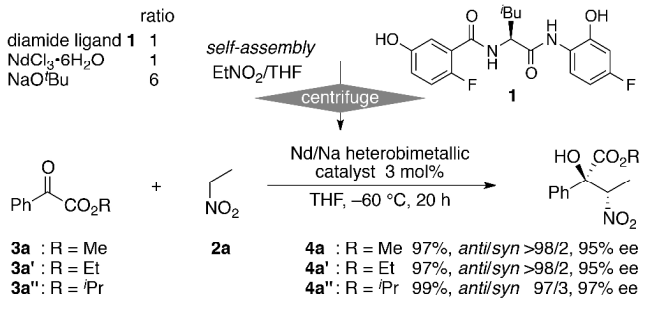
aromatic α-keto esters as viable substrates in this potentially useful catalytic process. Herein we report an *anti*-selective catalytic asymmetric nitroaldol reaction of α-keto esters with broad substrate generality (Scheme 1c). The Nd/Na heterobimetallic system worked as a solid-phase catalyst to furnish *anti*-configured products with high stereoselectivity. A strong

solvent effect was observed between structurally and physicochemically similar THF and 2-MeTHF, which was likely leveraged by the polymeric nature of the present catalyst complexes. This solid catalyst system was compatible with a flow reaction platform and the enantioenriched products obtained here contributed to the streamlined synthesis of the antifungal agents efinaconazole and albaconazole,[13] confirming the synthetic utility of the present catalytic system.

RESULTS and DISCUSSION

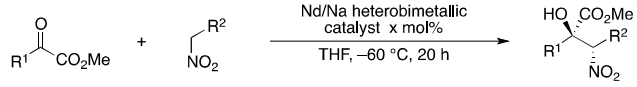
The leucine-derived diamide ligand **1** having fluorophenol units on both termini was specifically designed for the *anti*-selective asymmetric nitroaldol reaction with the combined use of Nd and Na cations. Simple mixing of **1**/$NdO_{1/5}(O^iPr)_{13/5}$/NaHMDS in THF led to the spontaneous formation of an insoluble catalyst via self-assembly that exhibited high catalytic performance as a solid-phase catalyst in nitroaldol reactions to aldehydes[12a, 12b] and α-trifluoromethyl ketones.[12e] The identification of inexpensive metal sources such as $NdCl_3$•$6H_2O$ and NaO^tBu to obtain similarly competent catalysts enhanced the practical aspects of this catalysis.[12c-e] This established system displayed high catalytic performance in a nitroaldol reaction of nitroethane **2a** and benzoyl formates **3a-a''**, as representative aromatic α-keto esters, affording the *anti*-configured and enantiomerically enriched tertiary *vic*-nitroalkanols **4a-a''** with high stereoselectivity, irrespective of the ester substituents (Scheme 2). The catalyst was broadly applicable to a range of α-keto esters **3** (Table 1). Intriguingly, the use of 2-Me-THF instead of THF as a solvent enhanced the reaction rate and generally afforded better stereoselectivity, enabling completion of the reaction with as little as 1 mol% of catalyst loading (entry 2). Aromatic α-keto esters bearing electron-donating alkyl and methoxy groups, and electron-withdrawing halogen and CF_3 groups were tolerated to give the desired nitroaldol adducts with high stereoselectivity (entries 5–21). Although the *o*-fluoro substituent was accommodated (entries 18,19), the catalytic system was sensitive to the steric factor and the *o*-Me group halted the catalysis.[14] Bulky substituents at the *p*-position were compatible with less satisfactory yield and stereoselectivity in the reaction using THF as the solvent (entries 9,11), but this was considerably improved by switching the solvent to 2-Me-THF (entries 10,12). Heteroaromatic substrates were successfully incorporated with high stereoselectivity (entries 22,23). Although the stereoselectivity was marginally lower, reactions using α-keto esters with alkynyl and alkyl substituents proceeded smoothly (entries 24–27), exemplifying the wide scope of the present catalysis. As for nitroalkanes, nitropropane **2b** and TBS-protected 2-nitroethanol **2c** exhibited acceptable reactivity, albeit with higher catalyst loading (9 mol%) (entries 28–31). The significantly enhanced yield and enantioselectivities of nitroaldol products **4la**, **4ma**, **4oa**, **4ab**, and **4ac** with 2-Me-THF are noteworthy (entries 21,23,27,29,31).

Scheme 2. Nitroaldol Reaction as a Powerful Tool for the Synthesis of *vic*-Amino Alcohols[a]



[a]**2a**: 1.2 mmol, **3**: 0.12 mmol. Catalyst amount was based on Nd used. Isolated yield is reported. Ee was determined by chiral stationary phase HPLC analysis.

Table 1. *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction of α-Keto Ester 3[a]



entry	α-keto ester R¹		nitroalkane R²		pdt	solvent	x	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	Ph	**3a**	Me	**2a**	**4a**	THF	3	97	>98/2	95
2						2-Me-THF	1	97	>98/2	99
3	2-naph	**3b**	Me	**2a**	**4ba**	THF	3	93	98/2	94
4						2-Me-THF	3	97	>98/2	99
5	3-MeC_6H_4	**3c**	Me	**2a**	**4ca**	THF	6	94	97/3	87
6						2-Me-THF	3	95	>98/2	98
7	4-MeC_6H_4	**3d**	Me	**2a**	**4da**	THF	6	94	>98/2	96
8						2-Me-THF	3	95	>98/2	99
9	4-PhC_6H_4	**3e**	Me	**2a**	**4ea**	THF	6	82	94/6	77
10						2-Me-THF	3	97	>98/2	99
11	4-$^tBuC_6H_4$	**3f**	Me	**2a**	**4fa**	THF	6	70	96/4	67
12						2-Me-THF	6	87	>98/2	93
13	3-$MeOC_6H_4$	**3g**	Me	**2a**	**4ga**	THF	6	90	97/3	90
14						2-Me-THF	3	93	>98/2	99
15	4-FC_6H_4	**3h**	Me	**2a**	**4ha**	THF	3	94	96/4	93
16	4-ClC_6H_4	**3i**	Me	**2a**	**4ia**	THF	6	94	98/2	93
17	4-BrC_6H_4	**3j**	Me	**2a**	**4ja**	THF	6	96	98/2	89
18	2,4-$F_2C_6H_3$	**3k**	Me	**2a**	**4ka**	THF	6	98	87/13	91
19						2-Me-THF	6	81	86/14	91
20	4-$CF_3C_6H_4$	**3l**	Me	**2a**	**4la**	THF	3	96	95/5	85
21						2-Me-THF	3	96	>98/2	98
22	2-thienyl	**3m**	Me	**2a**	**4ma**	THF	6	85	98/2	87
23						2-Me-THF	3	79	>98/2	96
24	TIPS-C≡C	**3n**	Me	**2a**	**4na**	THF	6	70	75/25	81
25						2-Me-THF	6	78	83/17	85
26	$PhCH_2CH_2$	**3o**	Me	**2a**	**4oa**	THF	9	81	79/21	46
27						2-Me-THF	9	81	88/12	92
28[e,f]	Ph	**3a**	Et	**2b**	**4ab**	THF	9	83	98/2	72
29[e,f]						2-Me-THF	9	96	>98/2	99
30[f,g]	Ph	**3a**	CH_2OTBS	**2c**	**4ac**	THF	9	19	84/16	<5
31[f,g]						2-Me-THF	9	71	91/9	81

[a]**2**: 1.2 mmol, **3**: 0.12 mmol. [b]Isolated yield of *anti*-diastereomer. [c]Determined by ^1H NMR of crude reaction mixture. [d]Determined by chiral stationary phase HPLC analysis. [e]Run at –78 °C. [f]Run for 48 h. [g]5 equiv of nitroalkane **2c** was used.

We next turned our attention to the unexpectedly large and beneficial solvent effect of 2-Me-THF. In terms of the physicochemical parameters and three-dimensional molecular structure, 2-Me-THF is between THF and Et_2O.[15] The reaction using Et_2O or other ethereal solvents, however, had markedly diminished stereoselectivity,[16] suggesting that THF molecules were partly involved as Lewis basic ligands in the key reaction steps. The profile of the reactions of **2a** and **3a** revealed significant rate enhancement (ca. 6.1-fold in the reaction of **3a** and **4b**) with 2-Me-THF (*vide supra*). Because 2-Me-THF possesses intrinsic chirality, we synthesized both (*R*)- and (*S*)-2-Me-THF to further dissect this intriguing solvent effect.[17] The first description of chemical reactions in chiral medium by Seebach in 1975 inspired the concept of chiral solvents in enantioselective reactions,[18] which was fostered synergistically

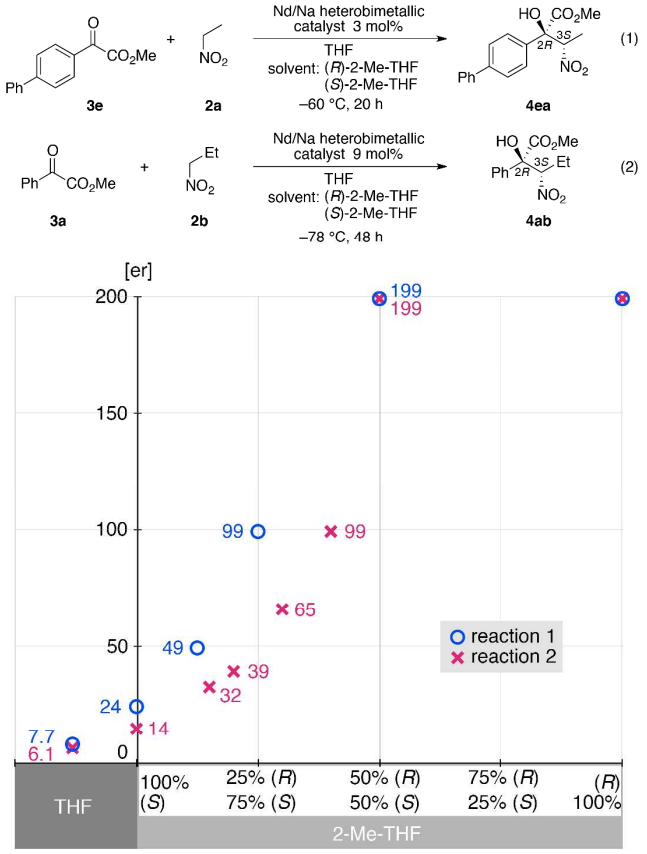


Figure 1. Nitroaldol reactions in different media, pure THF or 2-Me-THF with varied enantiomeric excess. Catalysts were prepared in a similar manner as shown in Scheme 2. In all cases, 10 equiv of nitroalkane was used and the reaction reached >80% (generally >95%) conversion after the designated reaction time and *anti*/*syn* ratio exceeds >20/1. Er denotes the enantiomeric ratio of the depicted (2*R*,3*S*)-isomer relative to the antipodal (2*S*,3*R*)-isomer. Reaction 1 in THF was performed with 6 mol% of catalyst.

with the development of ionic liquids as designer solvents.[19] Although a number of chiral ionic liquids have been disclosed as chiral reaction media and additives,[20] neutral chiral solvents have barely been explored due to the generally subtle effect on the reactions of interest.[21]

We selected two sets of reactions for in-depth study, **2a**+**3e** and **2b**+**3a**, where large deviations in enantioselectivity were detected depending on the selected solvent. These substrates were submitted to the reactions in partially enantiomerically enriched 2-Me-THF media, as illustrated in the plot of the enantiomeric excess of 2-Me-THF vs the enantiomeric ratio (er: major-(2*R*,3*S*)/minor-(2*S*,3*R*)) of the corresponding products **4ea** and **4ab** (Figure 1)**.** Significant enhancement of the enantiomeric excess (99% ee, er 199) became evident with racemic 2-Me-THF as shown in Table 1, and similar beneficial effects were obtained with enantiomerically pure (*R*)-2-Me-THF. In marked contrast, the reactions with enantiomerically pure (*S*)-2-Me-THF afforded the products with an enantiomeric ratio similar to that observed for THF. The enantiomeric ratio gradually increased with an increase in the fraction of

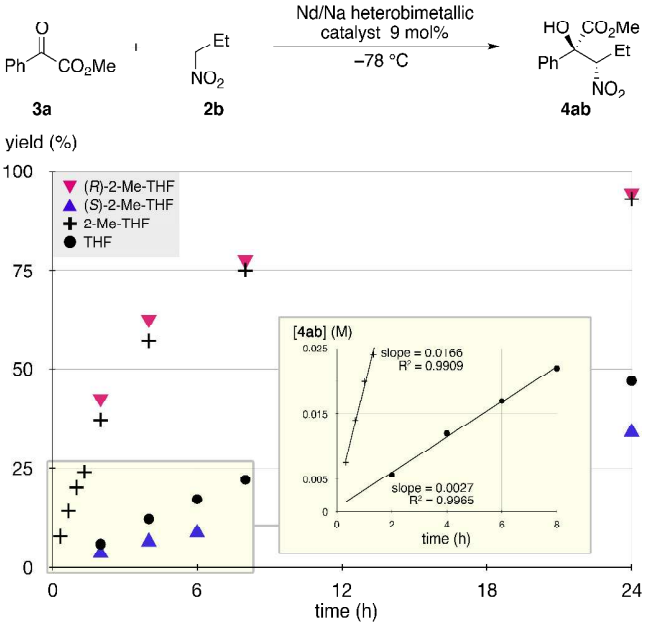


Figure 2. Reaction profile of **2b** and **3a** in different reaction media, THF, racemic 2-Me-THF, and enantiopure 2-Me-THF. 10 equiv of nitroalkane was used. Inset: initial rates of the reaction in THF (closed circle) and 2-Me-THF (plus), showing that the latter is 6.1-times faster.

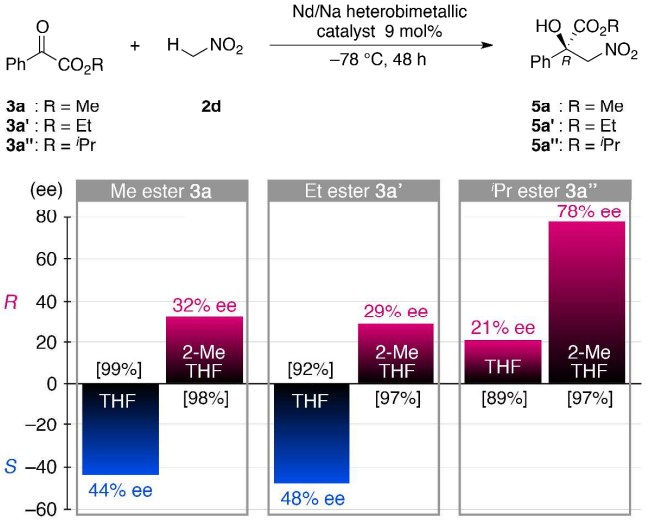


Figure 3. Divergent enantioselectivity in nitroaldol reaction of nitromethane **2d** and benzoyl formats **3a**–**a''**. 10 equiv of nitroalkane was used

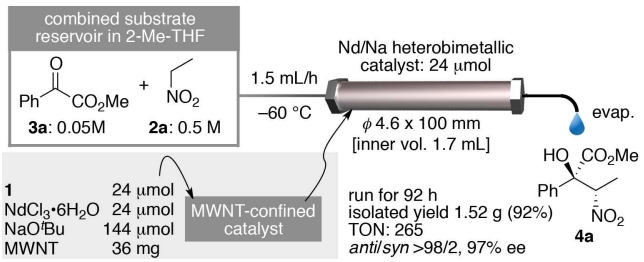
(*R*)-2-Me-THF over (*S*)-2-Me-THF in the reaction media, indicating that the Nd/Na catalyst responded to the chirality of the solvent molecules. Considering the positive dependency of the reaction rate on the concentration of the α-keto ester,[22] (*R*)-2-Me-THF was likely the matched dative ligand for the Nd/Na complex and played a key role in forming the desired (2*R*,3*S*)-enantiomer. When the solution was comprised of half (*R*)-2-Me-THF, i.e., racemic 2-Me-THF, the beneficial effect in the enantiomeric ratio was saturated, presumably because the

matched (*R*)-2-Me-THF had stronger affinity to the Nd/Na catalyst, which enhanced the enantioselectivity. This assumption is further supported by the observed reaction rate trend in the order of (*R*)-2-Me-THF > *rac*-2-Me-THF > THF > (*S*)-2-Me-THF (Figure 2), where the content of (*R*)-2-Me-THF dictated the rate acceleration. The notable difference in the reaction rate between THF and 2-Me-THF variants is intriguing, and is tentatively ascribed to the accessibility of the Nd cation as a Lewis acid to accept α-keto esters for C–C bond-forming events. Given the high coordination number of the rare earth Nd cation,[23] the sterically less demanding THF molecules might be more prone to occupy the coordination sphere, thereby retarding the reaction.

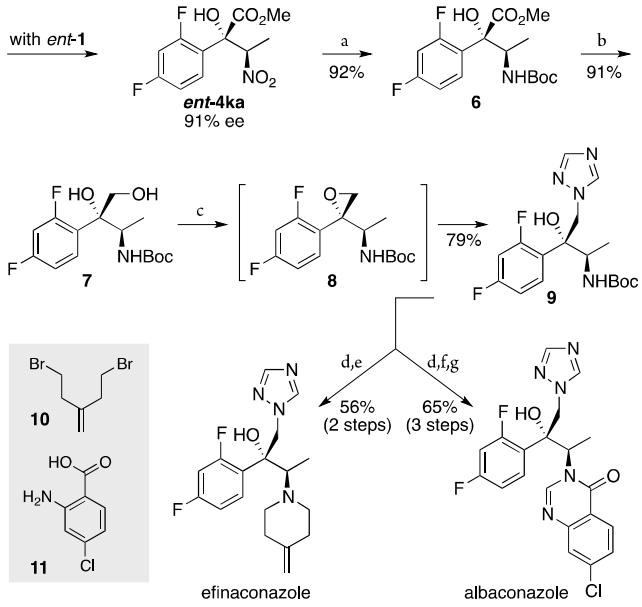
The solvent effects were further illustrated by the observed divergent enantioselectivity in the reaction of nitromethane **2d** (Figure 3). While the reaction of benzoyl formates **3a**–**a''** in 2-Me-THF consistently afforded the corresponding products **5a**–**a''** in an identical 2*R*-configuration, irrespective of the ester groups, the same reactions of methyl and ethyl esters in THF gave rise preferentially to the opposite 2*S*-configured products, indicating that 1) an extra methyl group of the metal nitronate of nitroethane **2a** played a pivotal role in controlling the prochiral-face selection of incoming α-keto esters; and 2) an extra methyl group of 2-Me-THF was juxtaposed in near proximity to direct α-keto esters to favor 2*R*-products. This assumption based on sterics is consistent with the different stereoselection trend observed with the bulkier isopropyl ester **3a''**; both THF and 2-Me-THF enhanced the formation of 2*R*-products, presumably due to the larger steric bias of the isopropyl group.

The heterogeneity of the Nd/Na catalyst was leveraged by implementing the present asymmetric catalysis in a continuous-flow reaction platform.[24] Flow reactions have been gaining increasing attention in industry as safer, more reproducible, and more scalable options over traditional batch conditions.[25] The application of asymmetric catalysis in a continuous-flow system is still limited largely due to the scarcity of reliable solid-phase asymmetric catalysts.[24f, 24h, 26, 27] Based on the carbon nanotube (CNT) confinement strategy, we previously demonstrated that simple mixing of multiwalled CNTs (MWNTs) in the catalyst preparation process produced the composite material of the MWNTs and the Nd/Na heterobimetallic catalyst, which proved to be a durable solid-phase catalyst competent for a continuous-flow reaction. We confirmed that this strategy was also valid for the reaction of α-keto esters. The substrate mixture (**2a** and **3a**) in 2-Me-THF was passed through a stainless-steel column charged with the

Scheme 3. *anti*-Selective Catalytic Asymmetric Nitroaldol Reaction of α-Keto Ester in a Continuous-Flow Platform



Scheme 4. Stereoselective Synthesis of Efinaconazole and Albaconazole



Reagents and conditions: (a) Pd/C, H_2, Boc_2O, MeOH, rt, 12 h, 92%; (b)$NaBH_4$, THF/MeOH, rt, 12 h, 91%; (c) NCCH=P^{n}Bu$_3$, 1,2,4-triazole, toluene, 80 °C, 3 h; after evaporation, K_2CO_3, DMF, 70 °C, 11 h, 79%; (d) 4 M HCl/1,4-dioxane, rt, 2 h; (e,) **10**, ^{i}Pr$_2$NEt, DMA, 80 °C, 24 h, 56% (2 steps); (f) **11**, EDCI•HCl, HOBt, 2,6-lutidine, DMF, rt, 24 h; (g) $Me_2NCH(OMe)_2$, MeOH, 70 °C, 24 h, 65% (3 steps).

MWNT-confined Nd/Na heterobimetallic catalyst. The desired product was obtained in 92% yield (1.52 g) after 92 h without any detrimental effect on stereoselectivity compared with batch conditions. Of note, the cooling volume was significantly reduced to decrease energy input for cryogenic conditions and evaporation of the eluents gave the crude product without any work-up procedure, resulting in an operationally simple protocol.

The utility of the present catalysis was demonstrated by a streamlined stereoselective synthesis of the marketed antifungal agents efinaconazole and albaconazole,[13] which share a key structural motif of 2,4-difluoroarylated *vic*-amino (*tert*-)alcohol (Scheme 4). The nitroaldol reaction of α-keto ester **3k** and nitroethane **2a** with antipodal ligand *ent*-**1** furnished *ent*-**4ka** bearing functionalities in a suitable stereochemistry. Facile reduction of the nitro group over Pd/C under hydrogen atmosphere followed by Boc protection gave **6** in 92% yield. Reduction of methyl ester with $NaBH_4$ gave diol **7**, to which 1,2,4-triazole was installed using Tsunoda's reagent (NCCH=P^{n}Bu$_3$)[28] via intermediary epoxide **8** to afford **9**. After deprotection of the Boc group, the exposed amine was captured by dibromide **10** to construct the requisite piperidine ring,[29] furnishing efinaconazole.[30] From the identical intermediate **9**, sequential amidation with 4-chloroantharanic acid **11** and subsequent condensation with *N*,*N*-dimethylformamide dimethyl acetal gave rise to a quinazolone, which was followed by condensation with orthoformate to deliver albaconazole.[31]

CONCLUSION

In summary, we developed an *anti*-selective asymmetric nitroaldol reaction of α-keto esters and nitroalkanes with broad substrate generality. A significant beneficial solvent effect of 2-Me-THF was observed and detailed study revealed that the Nd/Na heterobimetallic catalyst recognized its chirality. A continuous -flow reaction was successfully executed by taking advantage of the heterogeneity of the Nd/Na heterobimetallic catalyst. The utility of the present catalysis culminated in a streamlined stereoselective synthesis of the marketed antifungal agents efinaconazole and albaconazole.

ASSOCIATED CONTENT MATERIAL

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectroscopic data of new compounds (PDF)
NMR spectra (PDF)
Crystallographic data for compound **4a** (CIF)

AUTHOR INFORMATION

Corresponding Author

*Naoya Kumagai: nkumagai@bikaken.or.jp
*Masakatsu Shibasaki: mshibasa@bikaken.or.jp

ACKNOWLEDGMENT

This work was financially supported by ACT-C program (JPMJCR12YO) from JST and KAKENHI (17H03025 and 18H04276 in Precisely Designed Catalysts with Customized Scaffolding) from JSPS and MEXT. Dr. Tomoyuki Kimura is gratefully acknowledged for X-ray crystallographic analysis of **4a**. We are grateful to Dr. Ryuichi Sawa, Ms. Yumiko Kubota, and Dr. Kiyoko Iijima for NMR analysis.

REFERENCES

1. Henry, L. C. R. *Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.
2. (a) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315; (b) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561; (c) Blay, G.; Hernández-Olmos, V.; Pedro, J. *Synlett* **2011**, 1195.
3. (a) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388; (b) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894; (c) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595; (d) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem. Asian J.* **2007**, *2*, 1150; (e) Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903; (f) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682; (g) Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 484; (h) White, J. D.; Shaw, S. *Org. Lett.* **2012**, *14*, 6270; (i) Qin, D. D.; Yu, W.; Zhou, J. D.; Zhang, Y. C.; Ruan, Y. P.; Zhou, Z. H.; Chen, H. B. *Chem. Eur. J.* **2013**, *19*, 16541; (j) Kaldun, J.; Prause, F.; Scharnagel, D.; Freitag, F.; Breuning, M. *ChemCatChem* **2016**, *8*, 1846.
4. (a) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392; (b) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3230; (c) Sohtome, Y.; Kato, Y.; Handa, S.; Aoyama, N.; Nagawa, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2231; (d) Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 7562; (e) Lang, K.; Park, J.; Hong, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 1620; (f) Xu, K.; Lai, G.; Zha, Z.; Pan, S.; Chen, H.; Wang, Z. *Chem. Eur. J.* **2012**, *18*, 12357; (g) Li, Y.; Deng, P.; Zeng, Y.; Xiong, Y.; Zhou, H. *Org. Lett.* **2016**, *18*, 1578; (h) Blay, G.; Domingo, L. R.; Hernandez-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725; (i) Ube, H.; Terada, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895; (j) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Lett.* **2010**, *12*, 3058; (k) Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313; (l) Qiong ji, Y.; Qi, G.; Judeh, Z. M. A. *Eur. J. Org. Chem.* **2011**, 4892; (m) Boobalan, R.; Lee, G.-H.; Chen, C. *Adv. Synth. Catal.* **2012**, *354*, 2511; (n) Yao, L.; Wei, Y.; Wang, P.; He, W.; Zhang, S. *Tetrahedron* **2012**, *68*, 9119; (o) Arai, T.; Joko, A.; Sato, K. *Synlett* **2015**, 209.
5. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418.
6. (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222; (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875.
7. (a) Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433; (b) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167; (c) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712; (d) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2005**, *128*, 732; (e) Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. *J. Org. Chem.* **2007**, *72*, 9323; (f) Blay, G.; Hernandez-Olmos, V.; Pedro, J. R. *Org Biomol Chem* **2008**, *6*, 468; (g) Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* **2008**, *73*, 7373; (h) Cochi, A.; Métro, T.-X.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2010**, *12*, 3693; (i) Xu, H.; Wolf, C. *Synlett* **2010**, 2765; (j) Blay, G.; Hernandez-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2011**, *17*, 3768; (k) Judeh, Z.; Yao, Q.; Khong, D.; Gao, Q. *Synthesis* **2014**, *46*, 1793; (l) Grosseheilmann, J.; Bandomir, J.; Kragl, U. *Chemistry A European Journal* **2015**, *21*, 18957; (m) Li, Y.; Huang, Y.; Gui, Y.; Sun, J.; Li, J.; Zha, Z.; Wang, Z. *Org. Lett.* **2017**, *19*, 6416; (n) He, F.; Chen, G.; Yang, J.; Liang, G.; Deng, P.; Xiong, Y.; Zhou, H. *RSC Advances* **2018**, *8*, 9414; (o) Yamada, T.; Kuwata, M.; Takakura, R.; Monguchi, Y.; Sajiki, H.; Sawama, Y. *Adv. Synth. Catal.* **2018**, *360*, 637.
8. Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K. *Tetrahedron Lett.* **2008**, *49*, 1623.
9. Uraguchi, D.; Ito, T.; Nakamura, S.; Sakaki, S.; Ooi, T. *Chem. Lett.* **2009**, *38*, 1052.
10. Ref 9 labels the major diastereomer as *syn* considering that the ester group conforms the main skeleton. Herein, the R^1 group was considered as a group that conforms the main skeleton to give uniform *syn*/*anti* labeling for products derived from various electrophiles (aldehydes, α-CF_3 ketones, and α-keto esters).
11. Ref 7d describes preliminary data on the reaction of nitroethane and ethyl benzoylformate: dr = 4/1, 75% ee/88% ee (yield and identity of diastereomers were not given).
12. (a) Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860; (b) Ogawa, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6196; (c) Nonoyama, A.; Hashimoto, K.; Saito, A.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2016**, *57*, 1815; (d) Nonoyama, A.; Kumagai, N.; Shibasaki, M. *Tetrahedron* **2017**, *73*, 1517; (e) Karasawa, T.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2018**, *20*, 308.
13. Peyton, L. R.; Gallagher, S.; Hashemzadeh, M. *Drugs Today* **2015**, *51*, 705.
14. Only trace amounts of the product (if any) were obtained with α-keto ester bearing an o-tolyl group.
15. (a) Roderic P, Q.; Kester, D. E. *J. Organomet. Chem.* **1977**, *127*, 111; (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863; (c) Aycock, D. F. *Org. Proc. Res. Dev.* **2007**, *11*, 156.

16. In the reaction of **2a** and **3a** with 3 mol% of catalyst at –60 °C for 20 h; Et_2O: 99% yield, *anti*/*syn* 97/3, 65% ee; DME: 48% yield, *anti*/*syn* 90/10, 61% ee; CPME: 99% yield, *anti*/*syn* 95/5, 77% ee.
17. (*R*)- and (*S*)-2-Me-THF were synthesized by slight modification of the procedure reported in ref 21. See Supporting Information for details.
18. Seebach, D.; Oei, H. A. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 634.
19. (a) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772; (b) Wasserscheid, P.; Welton, T., *Ionic liquids in synthesis*. 2nd, completely rev. and enl. ed.; Wiley-VCH: Weinheim, 2007; (c) Hardacre, C.; Spivey, J. J.; Catalysis in ionic liquids: from catalyst synthesis to application. In *RSC catalysis series*, Royal Society of Chemistry: Cambridge, 2014.
20. (a) Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 6425; (b) Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 3921; (c) Ding, J.; Desikan, V.; Han, X.; Xiao, T. L.; Ding, R.; Jenks, W. S.; Armstrong, D. W. *Org. Lett.* **2005**, *7*, 335; (d) Wang, Z.; Wang, Q.; Zhang, Y.; Bao, W. *Tetrahedron Lett.* **2005**, *46*, 4657; (e) Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J.; Leitner, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 3689; (f) Chen, D.; Schmitkamp, M.; Francio, G.; Klankermayer, J.; Leitner, W. *Angew. Chem. Int. Ed.* **2008**, *47*, 7339.
21. For preliminary observation of the effect of chiral 2-Me-THF on stereoselectivity, see: Choi, Y. H.; Kwak, J.; Jeong, N. *Tetrahedron Lett.* **2009**, *50*, 6068.
22. See Supporting Information for details.
23. Cotton, S. A., *Lanthanide and actinide chemistry*. Wiley: Chichester, England; Hoboken, NJ, 2006.
24. For reviews of flow reactions, see: (a) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675; (b) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583; (c) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17; (d) Baxendale, I. R. *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519; (e) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849; (f) Tsubogo, T.; Ishiwata, T.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 6590; (g) Zhao, D.; Ding, K. *ACS Catal.* **2013**, *3*, 928; (h) Atodiresei, I.; Vila, C.; Rueping, M. *ACS Catal.* **2015**, *5*, 1972; (i) Munirathinam, R.; Huskens, J.; Verboom, W. *Adv. Synth. Catal.* **2015**, *357*, 1093; (j) Britton, J.; Raston, C. L. *Chem. Soc. Rev.* **2017**, *46*, 1250; (k) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796.
25. For reviews of the utility of flow reactions in therapeutic synthesis, see: (a) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2015**, *11*, 1194; (b) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. *Science* **2016**, *352*, 61; (c) Fitzpatrick, D. E.; Battilocchio, C.; Ley, S. V. *ACS Cent. Sci.* **2016**, *2*, 131; (d) Kobayashi, S. *Chem. Asian J.* **2016**, *11*, 425; (e) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2.
26. For reviews of asymmetric flow catalysis, see: (a) Mak, X. Y.; Laurino, P.; Seeberger, P. H. *Beilstein J. Org. Chem.* **2009**, *5*, 19; (b) Ishitani, H.; Saito, Y.; Kobayashi, S. *Top. Organomet. Chem.* **2016**, *57*, 213.
27. For leading examples of the utility of flow catalysis for streamlined synthesis of therapeutics, see: (a) Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329; (b) Ziegler, R. E.; Desai, B. K.; Jee, J. A.; Gupton, B. F.; Roper, T. D.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2018**, *57*, 7181.
28. (a) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081; (b) Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2531; (c) Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Ito, S. *Tetrahedron Lett.* **1996**, *37*, 2463.
29. (a) Xu, X. Preparation of efinaconazole. CN Patent: 104327047, Oct 17, 2014; (b) Bao, J.; Huang, Y.; Ding, W.; Jiang, Y.; Zhang, X. Synthetic method of efinaconazole and intermediate thereof. CN Patent: 104292214 A, Sep 24, 2014.
30. (a) Ogura, H.; Kobayashi, H.; Nagai, K.; Nishida, T.; Naito, T.; Tatsumi, Y.; Yokoo, M.; Arika, T. *Chem. Pharm. Bull.* **1999**, *47*, 1417; (b) Tatsumi, Y.; Yokoo, M.; Arika, T.; Yamaguchi, H. *Antimicrob. Agents Chemother.* **2001**, *45*, 1493; (c) Tatsumi, Y.; Nagashima, M.; Shibanushi, T.; Iwata, A.; Kangawa, Y.; Inui, F.; Siu, W. J. J.; Pillai, R.; Nishiyama, Y. *Antimicrob. Agents Chemother.* **2013**, *57*, 2405; (d) Tamura, K.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2014**, *79*, 3272.
31. Bartroli, J.; Turmo, E.; Algueró, M.; Boncompte, E.; Vericat, M. L.; Conte, L.; Ramis, J.; Merlos, M.; Garćıa-Rafanell, J.; Forn, J. *J. Med. Chem.* **1998**, *41*, 1869.