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Heterogeneous Heterobimetallic Catalysis Enabling Expeditious Access to CF_3-Containing *vic*-Amino Alcohols

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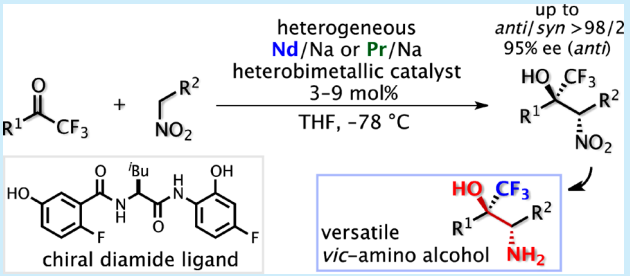
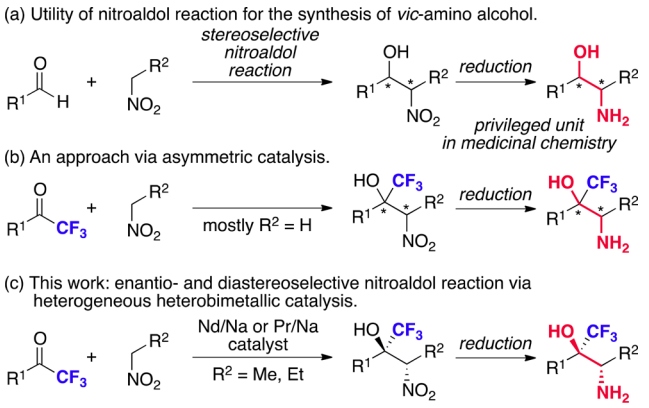
Supporting Information

ABSTRACT: A highly *anti*-selective catalytic asymmetric nitroaldol reaction of trifluoromethyl ketones based on Nd/Na and Pr/Na heterobimetallic catalysts was developed. These catalysts function as heterogeneous catalysts to engage nitroethane and a range of trifluoromethyl ketones in a stereoselective assembly to afford CF_3-appended *vic*-nitroalkanols that could be readily converted to enantioenriched *vic*-amino alcohols, which are privileged structural motifs in medicinal chemistry.



The catalytic asymmetric nitroaldol (Henry) reaction has established its unwavering position as a high-fidelity carbon−carbon bond-forming reaction with a high level of stereochemical control.[1,2] The requisite nitroalkane pronucleophiles are readily available and reactive under mild conditions, allowing for atom-economical reaction settings in which a simple proton transfer drives the catalysis. Because the nitroaldol adducts (*vic*-nitroalkanols) are direct precursors of *vic*-amino alcohols, which are privileged structural motifs in medicinal chemistry, considerable effort has been devoted to this specific transformation (Scheme 1a).[3−5]

Scheme 1. Access to CF_3-Containing *vic*-Amino Alcohols via Nitroaldol Reaction



As the methodology enabling the incorporation of fluorine atoms into active pharmaceutical ingredients (APIs) has attracted growing attention,[6] several approaches have been developed to apply the nitroaldol reaction manifold to produce enantioenriched fluorine-containing *vic*-amino alcohols (Scheme 1b).[7] Saá and co-workers were the first to report an enantioselective addition of nitromethane to trifluoromethyl ketones via La(III) catalysis,[8] furnishing enantioenriched *vic*-nitroalkanols possessing an α-CF_3 tertiary alcohol unit. The tertiary alcohol substructure contains a tetrasubstituted stereogenic center[9] that is not accessible via the well-established hydrogenation methodology. Although strategic use of the nitroaldol reaction to access this class of chiral building blocks is noteworthy, the need for a 25 mol % loading of La(III) complex (and a 3-fold excess of a chiral ligand relative to La(III)) with a 25 mol % loading of proton sponge as a base and a long reaction time poses limitations, leaving much room for improvement toward a more practical synthesis of CF_3-appended *vic*-amino alcohols. A couple of organocatalysts[10] and metal-based catalysts[11] were developed for the nitroaldol arsenal to engage nitromethane in an enantioselective addition to trifluoromethyl ketones, but the implementation of higher nitroalkanes is less well explored. Xu and Wolf[11a] reported the only example utilizing nitroethane with a 10 mol % loading of a Cu(II)/bisoxazolidine complex and 20 mol % Bu_3N, displaying four different examples ranging from 77−89% de and 78−91% ee. Herein we report a general *anti*-selective nitroaldol reaction using nitroethane and nitropropane with high enantio- and diastereoselectivity (Scheme 1c). Heterogeneous catalysts comprising an amide-based ligand and Nd/Na or Pr/Na bimetallic salts were competent to promote the reaction with catalyst loadings of 3−9 mol %.

We planned a stereoselective assembly of 2,2,2-trifluoroacetophenone (**2a**) and nitroethane (**3a**) as a representative trifluoromethyl ketone and nitroalkane, respectively, which were submitted to a reaction with the heterogeneous Nd/Na heterobimetallic catalyst identified by our group (Table 1).[12] The characteristic features of this heterobimetallic complex are (1) the spontaneous formation of an insoluble catalyst

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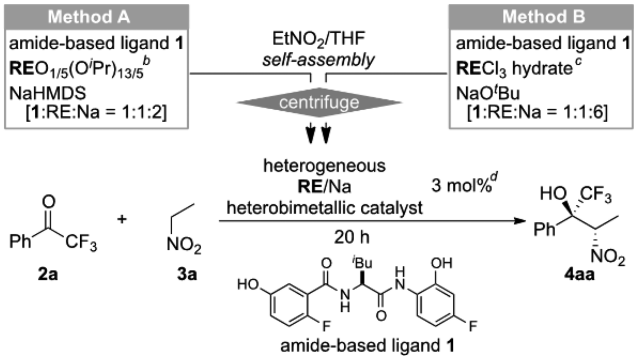
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. *Anti*-Selective Catalytic Asymmetric Nitroaldol Reaction of Nitroethane (3a) with 1,1,1-Trifluoroacetophenone (2a)[a]



entry	RE	method	solvent	T (°C)	yield (%)[e]	*anti*/*syn*[f]	ee (*anti*) (%)[g]
1	Nd	A	THF	−40	99	90/10	76
2	Nd	A	THF	−60	92	93/7	85
3	Nd	A	THF	−78	90	96/4	93
4	Nd	B	THF	−78	95	95/5	92
5	Nd	B	Et_2O	−78	84	84/16	90
6	Nd	B	DME	−78	trace	—	—
7	Nd	B	CPME	−78	62	92/8	82
8	Nd	B	2-Me-THF	−78	70	92/8	84
9[h]	La	A	THF	−78	trace	—	—
10	Pr	A	THF	−78	92	97/3	95
11	Pr	B	THF	−78	91	96/4	94
12[h]	Sm	A	THF	−78	12	—	56
13[h]	Gd	A	THF	−78	trace	—	—
14[h]	Dy	A	THF	−78	trace	—	—
15[h]	Er	A	THF	−78	trace	—	—
16[h]	Yb	A	THF	−78	trace	—	—

[a]**2** (0.12 mmol), **3a** (1.2 mmol). Isolated yields are shown. RE denotes rare-earth metal. [b]For Pr, Dy, Er, and Yb, RE(O^iPr)$_3$ was used. [c]$NdCl_3 \cdot 6H_2O$ or $PrCl_3 \cdot 7H_2O$. [d]Based on RE salts used for catalyst preparation. [e]Determined by ^{1}H NMR analysis of the crude mixtures with mesitylene as an internal standard. [f]Determined by ^{1}H NMR analysis. [g]Determined by HPLC analysis. [h]The catalyst mixture did not form a heterogeneous complex, and the resulting homogeneous mixture was used as catalyst.

from amide-based ligand **1**, NdO$_{1/5}$(O^iPr)$_{13/5}$, and NaHMDS via self-assembly (method A)[13] and (2) the competence of the thus-formed solid material as a heterogeneous catalyst in ethereal solvents to promote the nitroaldol reaction with aldehydes in an *anti*- and enantioselective manner. Given the unparalleled efficiency of the **1**/Nd/Na complex toward the deprotonative activation of nitroalkanes and stereochemical control of the nitronate addition, we reasoned that this heterogeneous catalysis would be proficient in the addition to trifluoromethyl ketones **2**. The heterogeneous catalyst isolated by centrifugation was used for the reaction. Gratifyingly, suitable catalytic conditions quickly emerged by slight modification of the previously identified conditions to give the *anti*-configured product **4aa** with high stereoselectivity. Little or no retro reaction was observed, and the stereoselectivity, which was kinetically determined, displayed the ordinary dependence on the reaction temperature (entries 1−3). Because of the limited availability and high cost of NdO$_{1/5}$(O^iPr)$_{13/5}$/NaHMDS (method A), catalyst preparation using $NdCl_3 \cdot 6H_2O$/NaO^{t}Bu (method B) was more favorable and exhibited almost identical catalytic performance (entries 3 and 4). The reaction settings were more sensitive to the solvent than the reactions with aldehydes, and THF was an indispensable solvent among ethereal solvents (entries 4−8). Screening of rare-earth metal (RE) alkoxides revealed that the Pr/Na bimetallic system was also competent in the present reaction, while other RE/Na systems failed in the reaction (entries 4, 9, 10, and 12−16). The stereochemical outcomes were highly dependent on the reaction temperature, and the reaction reached completion with the highest stereoselectivity at −78 °C. For the Pr/Na catalytic system, catalyst preparation using inexpensive $PrCl_3 \cdot 7H_2O$ instead of Pr(O^iPr)$_3$ was valid and provided similar reaction outcomes (entries 10 and 11). On the basis of their similar ionic radii, coordination characteristics, and Lewis acidity, the Nd/Na and Pr/Na heterobimetallic complexes likely shared a similar three-dimensional architecture responsible for both the catalytic activity and stereoselectivity.[14]

The scope of the nitroaldol reaction using a range of trifluoromethyl ketones **2** with the catalyst prepared via method B is displayed in Scheme 2. The reaction was scalable to obtain 1.2 g of *anti*-configured *vic*-nitroalkanol **4aa** bearing an α-CF$_3$ tertiary alcohol unit. Despite the fact that the *o*-substituted trifluoromethyl ketone exhibited significantly diminished reactivity, the *m*,*p*-substitution was accommodated even with a *t*-Bu group (**4ba**−**da**), and the Pr/Na catalyst exhibited similar catalytic performance. Other nonfunctionalized and *p*-halo-substituted ketones produced the desired adducts with high stereoselectivity (**4ea**−**ha**). While the electron-donating *m*-OMe-substituted ketone had a slightly eroded yield and stereoselectivity with the Nd/Na catalyst, the Pr/Na catalyst provided a superior reaction outcome,

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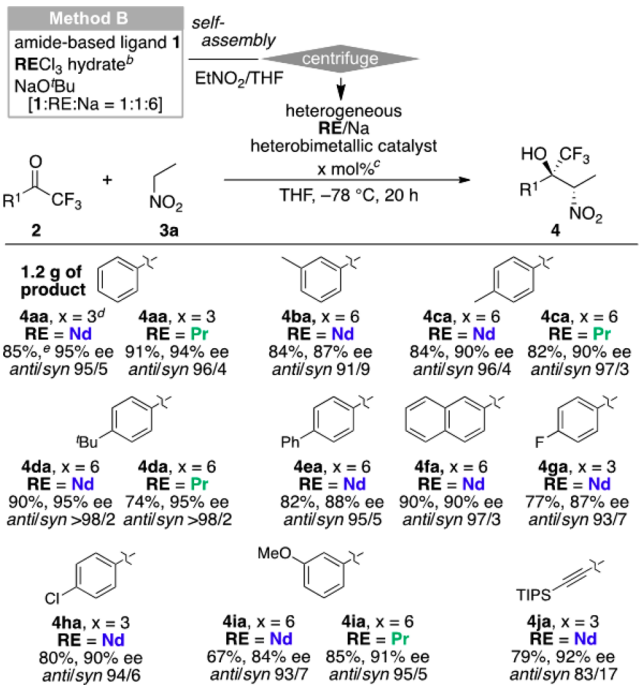
Scheme 2. *Anti*-Selective Catalytic Asymmetric Nitroaldol Reaction of Nitroethane (3a) with Trifluoromethyl Ketones 2[a]

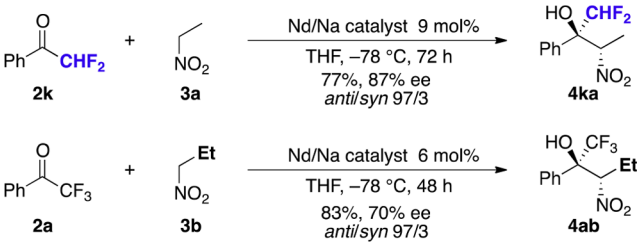


[a]**2** (0.12 mmol), **3a** (1.2 mmol). Isolated yields of *anti* diastereomers are shown. RE denotes rare-earth metal. [b]$NdCl_3 \cdot 6H_2O$ or $PrCl_3 \cdot 7H_2O$. [c]Based on $RECl_3$ hydrate used for catalyst preparation. [d]**2a** (5.74 mmol, 1.0 g), **3a** (57.4 mmol). [e]Isolated yield of the *anti* diastereomer.

presumably because the small deviation in the structural parameters of the catalyst was beneficial for higher stereoselectivity as well as for catalytic efficiency (**4ia**). Notably, trifluoromethyl ynone served as a suitable substrate to give desired adduct **4ja** bearing a propargylic tertiary alcohol unit that could be used as a convenient chiral building block for further elaboration.[15] Intriguingly, difluoromethyl ketone **2k** could be transformed to the desired nitroaldol adduct **4ka** with the Nd/Na catalyst with high stereoselectivity, although a catalyst loading of 9 mol % (method B) and extended reaction times were essential because of the low electrophilicity (Scheme 3a). An attempt to use nitropropane (**3b**) as the pronucleophile produced **4ab** in a highly *anti*-selective manner, albeit with eroded enantioselectivity (Scheme 3b).[16]

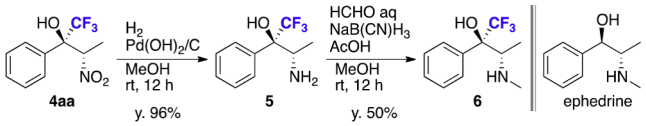
The utility of the present catalytic asymmetric protocol was demonstrated by the enantioselective synthesis of CF_3-decorated ephedrine **6** (Scheme 4).[17] The nitroaldol adduct

Scheme 3. Extended Scope: Reaction with Difluoromethyl Ketone 2k or Nitropropane (3b)



anti-**4aa** (93% ee) was submitted to hydrogenation over $Pd(OH)_2/C$ to give *vic*-amino alcohol **5** in an excellent yield without compromising the stereochemical integrity. Reductive amination with formalin and $NaB(CN)H_3$ afforded **6**, sharing the overall architecture of ephedrine except having an appended CF_3 group on the tertiary alcohol moiety.

Scheme 4. Enantioselective Synthesis of CF_3-Appended Ephedrine 6



In conclusion, we have developed an *anti*-selective catalytic asymmetric nitroaldol reaction of trifluoromethyl ketones and nitroethane. The Nd/Na or Pr/Na heterobimetallic catalyst ligated with a chiral diamide promoted the reaction with high stereoselectivity, allowing for expeditious access to enantioenriched *vic*-nitroalkanols with an α-CF_3 tertiary alcohol unit. The facile reduction to the corresponding *vic*-amino alcohol as well as the enantioselective synthesis of CF_3-appended ephedrine highlight the potential utility of the reaction in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03767.

Experimental procedures, spectroscopic data for new compounds, and NMR spectra (PDF)

Accession Codes

CCDC 1587722 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(13) Nitroethane was also used for complexation and may be an indispensable component of the solid catalyst, as evidenced by HRMS analysis. See ref 12b for details.
(14) The catalyst without Nd or Pr (ligand **1**/NaO^{t}Bu = 1/6) led to no reaction, indicating that the heterobimetallic complex was of prime importance for reaction progress as well as stereoselectivity.
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(16) Although **3a** was used for catalyst preparation and was likely included in the thus-formed heterogeneous catalyst after centrifugation, the amount of added **3b** in the reaction mixture was significantly higher, and no product derived from **3a** was observed.
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