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Nonsilyl bicyclic secondary amine catalyzed Michael addition of nitromethane to β,β-disubstituted α,β-unsaturated aldehydes†

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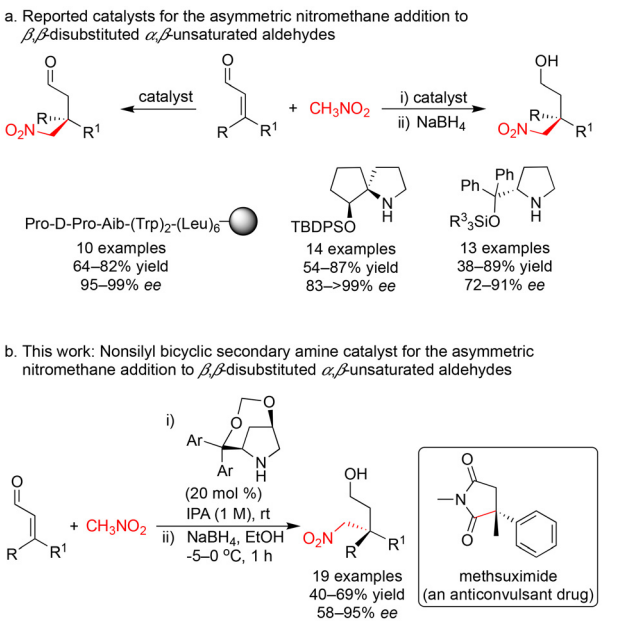
The asymmetric Michael addition of nitroalkanes to β,β-disubstituted α,β-unsaturated aldehydes is a useful method for the construction of all-carbon quaternary stereocenters. Nonsilyl bicyclic secondary amine organocatalysts were employed in reactions involving a wide range of β,β-disubstituted α,β-unsaturated aldehydes with nitroalkanes to achieve products with all-carbon quaternary stereocenters in up to 69% yield and 95% ee. The scalability of this methodology was demonstrated at the 5.1 mmol scale. The synthetic utility of this methodology is showcased through the concise asymmetric synthesis of methsuximide, an anticonvulsant drug.

Introduction

The asymmetric synthesis of molecules bearing all-carbon quaternary stereocenters remains one of the challenging tasks in synthetic organic chemistry.[1] Interestingly, this methodology finds potential applications in the total synthesis of natural products and pharmaceutical drugs.[2] The Michael addition of carbon nucleophiles to β,β-disubstituted α,β-unsaturated carbonyl compounds is one of the elegant methods to access molecules with all-carbon quaternary stereocenters.[3] Nevertheless, the Michael addition of nitromethane to β,β-disubstituted α,β-unsaturated aldehydes has been comparatively underexplored (Scheme 1a).[4] Kudo and Akagawa reported an undecapeptide-catalyzed asymmetric Michael addition of nitromethane to β,β-disubstituted α,β-unsaturated aldehydes, affording aldehydes bearing β-quaternary carbon stereocenters.[4a] Tu and co-workers developed a spiro-pyrrolidine catalyst for the same transformation, followed by reduction using $NaBH_4$, yielding alcohols with all-carbon quaternary stereocenters.[4b] Although the above two methodologies offer products in moderate to good yields and excellent enantioselectivities, the synthesis of these catalysts involves multistep tedious processes. Hayashi and co-workers demonstrated an asymmetric Michael addition of nitromethane to β,β-disubstituted α,β-unsaturated aldehydes using the Hayashi–Jørgensen catalyst, providing aldehydes with β-quaternary carbon stereocenters.[4c,d] Although the trimethylsilyl ether group in Hayashi–Jørgensen catalysts plays a crucial role in achieving high enantioselectivity of products, its stability in the presence of acid additives[5a,b] and reagents[5c] is a concern. Recently, we reported the synthesis of a nonsilyl bicyclic secondary amine catalyst, derived from 4-hydroxy-L-proline in four steps, which was utilized for the asymmetric transfer hydrogenation of β,β-disubstituted α,β-unsaturated aldehydes.[6] Herein, we disclose the nonsilyl bicyclic secondary amine-catalyzed asymmetric Michael addition of nitromethane



Scheme 1 Asymmetric Michael addition of nitromethane to β,β-disubstituted α,β-unsaturated aldehydes.

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to β,β-disubstituted α,β-unsaturated aldehydes. Furthermore, we demonstrate the synthetic utility of this methodology for the concise asymmetric synthesis of methsuximide,[7] an anticonvulsant drug (Scheme 1b).

Results and discussion

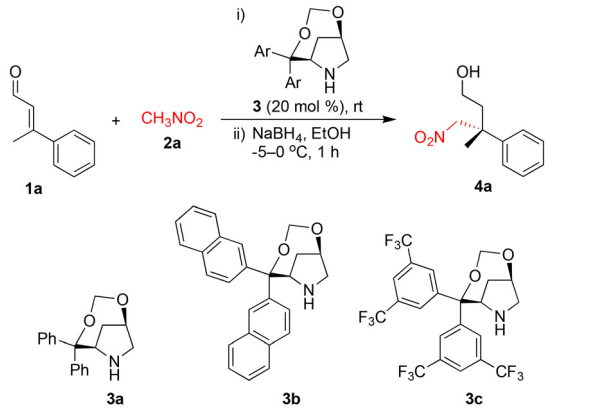
Initially, β-methyl cinnamaldehyde **1a** was treated with nitromethane **2a** (10 equiv.) in the presence of the nonsilyl bicyclic secondary amine catalyst **3a** (20 mol%) under neat reaction conditions at rt for 72 h to afford the Michael adduct. For characterization purposes, the crude product was reduced *in situ* using $NaBH_4$ in EtOH at −5 to 0 °C, furnishing alcohol **4a** in 20% isolated yield with 88% ee (Table 1, entry 1).

Among the solvents screened (Table 1, entries 2–12), protic solvents were found to be effective, offering shorter reaction times and improved product yields (Table 1, entries 5–12). Notably, the reaction carried out in IPA (isopropanol) was completed in 36 h, affording product **4a** in 69% isolated yield with 95% ee (Table 1, entry 7). Attempts to either decrease (Table 1, entry 13) or increase (Table 1, entry 14) the equivalents of nitromethane **2a** were not fruitful. The addition of benzoic acid (20 mol%) to the reaction led to a longer reaction time, which in turn resulted in decreased product yield and enantioselectivity (Table 1, entry 15). This decline is attributed to product decomposition occurring over the prolonged reaction time. Traces of product **4a** were observed upon lowering the reaction temperature to 0 °C (Table 1, entry 16). The reaction with 10 mol% of catalyst **3a** took a longer time (96 h), affording product **4a** in 53% yield and 93% ee (Table 1, entry 17). When catalyst **3a** was replaced with **3b** or **3c** under the same reaction conditions, lower product yield and enantioselectivity were observed (Table 1, entries 18 and 19).

After the successful reaction optimization for the asymmetric Michael addition of nitromethane **2a** to β-methyl cinnamaldehyde **1a** (Table 1, entry 7), the substrate scope was investigated, as shown in Scheme 2. The β-aryl α,β-unsaturated aldehydes **1b–1e** containing electron-donating groups (*p*-OMe, *p*-Me, *p*-Cl and *p*-F) at the *para*-position of the aryl ring smoothly underwent Michael addition with nitromethane **2a** to give the corresponding alcohols **4b–4e** in 48–61% yields and 91–95% ees. Similarly, substrates **1f** and **1g** containing electron-withdrawing groups (*p*-NO_2 and *p*-CF_3, respectively) at the *para*-position also participated effectively in the reaction, providing alcohols **4f** and **4g** in 61% yield and 91% ee and in 45% yield and 92% ee, respectively. Substrates **1h** and **1k** with *meta*-substituted aryl groups, including electron donating groups (*m*-OMe or *m*-Me) and electron-withdrawing groups (*m*-NO_2 or *m*-CF_3), also participated in the transformation efficiently under the optimized reaction conditions to afford the corresponding alcohols **4h** and **4k** in moderate to good yields and excellent enantioselectivities. β-Aryl α,β-unsaturated aldehydes bearing biphenyl (**1l**) and 2-naphthyl (**1m**) substituents at the β-position provided alcohols **4l** and **4m** in 50% yield and 93% ee and in 52% yield and 94% ee, respectively. Notably, a heteroaromatic substrate bearing a 2-thiophenyl substituent (**1n**) was well tolerated, affording alcohol **4n** in 47% yield and 95% ee. When the β-ethyl β-phenyl α,β-unsaturated aldehyde **1o** was studied for the Michael addition of nitromethane **2a**, alcohol **4o** was obtained in 40% yield and 88% ee. The Michael addition of nitromethane **2a** to the 2-oxoindoline-3-ylidene acetaldehyde **1p** was not effective under the optimized reaction conditions.[8] Interestingly, the use of catalyst **3c** (20 mol%) facilitated the reaction, affording alcohol **4p** in 51% yield and 87% ee.

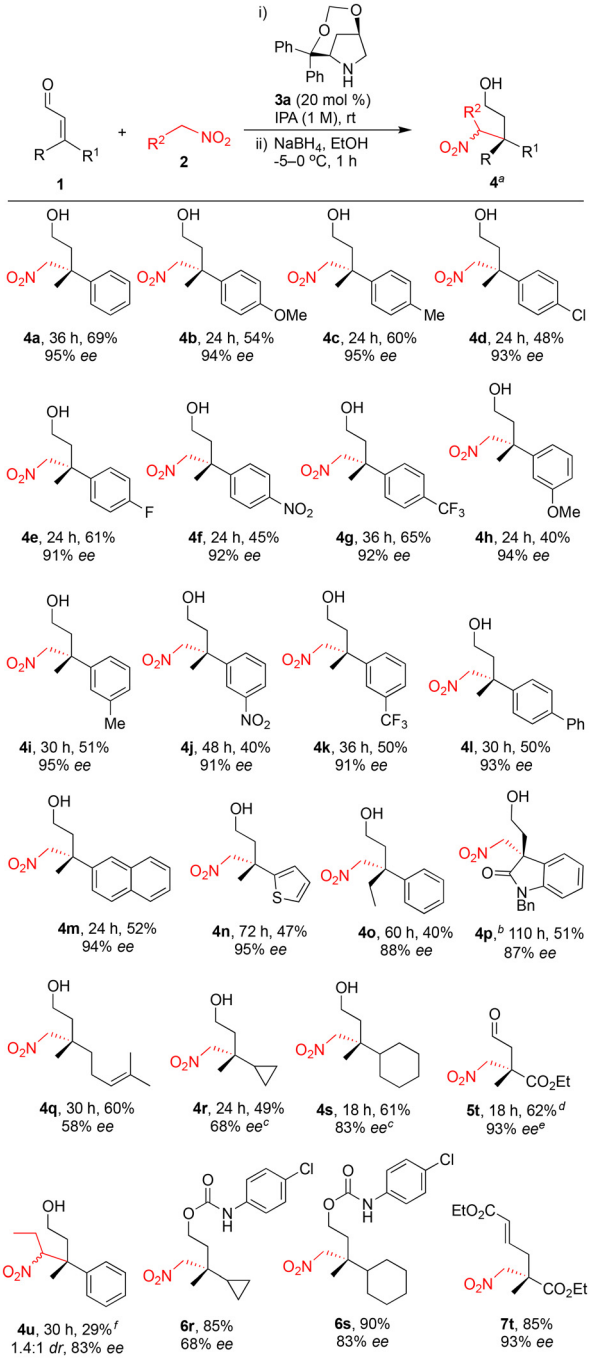
This methodology was also applied to the β,β-dialkyl α,β-unsaturated aldehydes **1q–1s** to obtain alcohols **4q–4s** in 49–61% yields and 58–83% ees. The enantiomeric excesses of alcohols **4r** and **4s** were determined after converting them to

Table 1 Optimization of the reaction conditions[a]

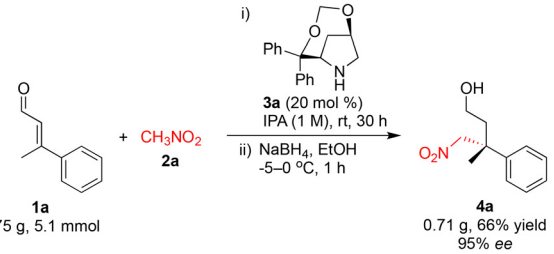


Entry	Cat.	Solvent	*t* (h)	Yield[b] (%)	ee[c] (%)
1	**3a**	Neat	72	20	88
2	**3a**	CH_2Cl_2	120	21	90
3	**3a**	Toluene	72	25	93
4	**3a**	CH_3CN	120	16	45
5	**3a**	MeOH	24	30	91
6	**3a**	EtOH	54	59	93
7	**3a**	IPA	36	69	95
8	**3a**	*t*-BuOH	24	60	95
9	**3a**	$(CH_2OH)_2$	30	64	94
10	**3a**	Glycerol	48	65	94
11	**3a**	$HO(CH_2)_4OH$	48	62	91
12	**3a**	TFE	24	60	88
13[d]	**3a**	IPA	30	40	91
14[e]	**3a**	IPA	48	59	93
15[f]	**3a**	IPA	92	40	91
16[g]	**3a**	IPA	48	Trace	nd
17[h]	**3a**	IPA	96	53	93
18	**3b**	IPA	48	35	91
19	**3c**	IPA	50	48	91

[a] Reactions were performed with **1a** (29 mg, 0.2 mmol, 1 equiv.), CH_3NO_2 **2a** (107 μL, 2.0 mmol, 10 equiv.) and catalyst **3** (0.04 mmol, 20 mol%) in solvent (0.2 mL, 1.0 M) at rt followed by reduction to the corresponding alcohol **4a** using $NaBH_4$ (76 mg, 2.0 mmol, 10 equiv.) in EtOH (2.5 mL), unless otherwise noted. [b] Isolated yield after column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] CH_3NO_2 (53 μL, 1.0 mmol, 5 equiv.) was used. [e] CH_3NO_2 (214 μL, 4.0 mmol, 20 equiv.) was used. [f] Benzoic acid (5 mg, 0.04 mmol, 20 mol%) was added. [g] Reaction was performed at 0 °C. [h] Catalyst **3a** (6 mg, 0.02 mmol, 10 mol%) was used. IPA = isopropanol; nd = not determined; TFE = trifluoroethanol.



Scheme 2 Substrate scope. [a] Reactions were performed with **1** (0.2 mmol, 1 equiv.), nitroalkane **2** (2.0 mmol, 10 equiv.) and catalyst **3a** (11 mg, 0.04 mmol, 20 mol%) in IPA (0.2 mL, 1.0 M) at rt followed by reduction to the corresponding alcohol **4** using $NaBH_4$ (76 mg, 2.0 mmol, 10 equiv.) in EtOH (2.5 mL), unless otherwise noted. [b] Catalyst **3c** (22 mg, 0.04 mmol, 20 mol%) was used. [c] Enantiomeric excess was determined after converting alcohols **4r** and **4s** to the carbamate derivatives **6r** and **6s**, respectively, using 4-chlorophenyl isocyanate. [d] Reaction was performed in EtOH (1.0 M). [e] Enantiomeric excess was determined after converting aldehyde **5t** to diester **7t** using ethyl(triphenylphosphoranylidene)acetate. [f] Reaction was performed under neat conditions.



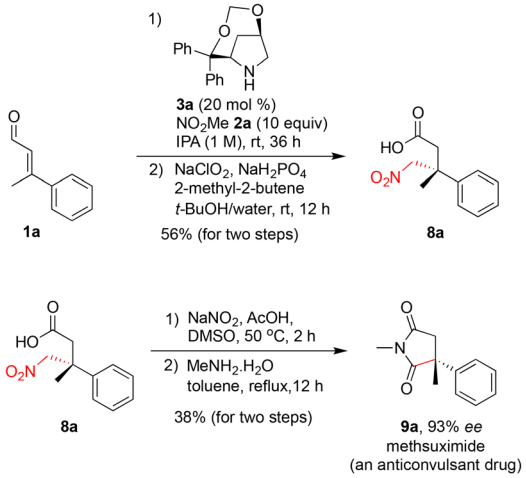
Scheme 3 Scale-up synthesis of alcohol **4a**.

the corresponding carbamate derivatives **6r** (85% yield and 68% ee) and **6s** (90% yield and 83% ee), respectively, using 4-chlorophenyl isocyanate and Et_3N in CH_2Cl_2 (see the ESI†). The reaction of nitromethane **2a** with substrate **1t** containing an ester group at the β-position proceeded very slowly in IPA. However, when the reaction was carried out in EtOH, completion was achieved in 18 h, affording aldehyde **5t** in 62% yield and 93% ee. The enantiomeric excess of aldehyde **5t** was determined after converting it to diester **7t** (85% yield and 93% ee) using ethyl(triphenylphosphoranylidene)acetate (see the ESI†). The reaction of nitropropane **2b** with β-methyl cinnamaldehyde **1a** in the presence of catalyst **3a** under neat conditions (as the reaction in IPA was very slow) yielded product **4u** as an inseparable mixture of diastereomers in 29% yield with 1.4 : 1 dr and 83% ee. The absolute configuration of products **4a–4u** was assigned based on the comparison of the optical rotation values of products **4a**, **4b**, **4f**, **4p** and **4q** with those reported in the literature.[4b]

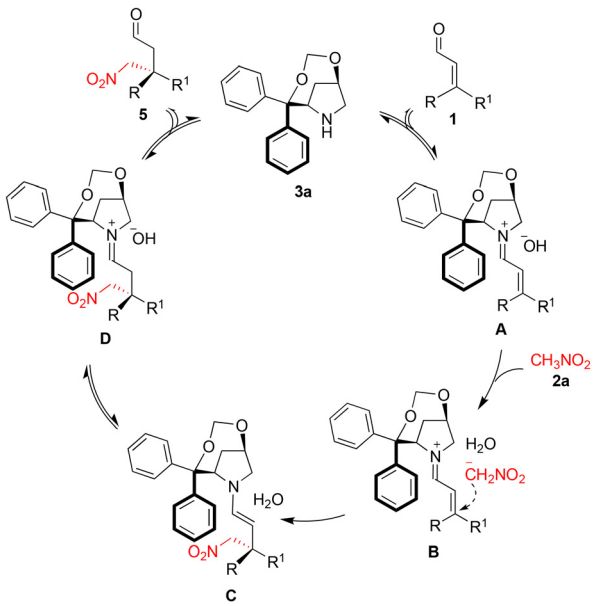
To showcase the scalability of the methodology, 5.1 mmol of β-methyl cinnamaldehyde **1a** was subjected to the optimized reaction conditions, affording alcohol **4a** in 66% yield and 95% ee (Scheme 3).

To demonstrate the application of this methodology, a concise asymmetric synthesis of methsuximide, an anticonvulsant drug, was envisaged starting from β-methyl cinnamaldehyde **1a**, as shown in Scheme 4. The Michael addition of nitromethane **2a** to β-methyl cinnamaldehyde **1a** catalyzed by **3a** in IPA furnished the corresponding Michael adduct, which was subsequently oxidized to carboxylic acid **8a** *via* Pinnick oxidation (56% yield over two steps). Furthermore, the nitro group in compound **8a** was converted to a carboxylic acid using $NaNO_2$ and acetic acid in DMSO, yielding the corresponding dicarboxylic acid. Condensation of this intermediate with methylamine in toluene under reflux conditions afforded methsuximide **9a** in 38% yield over two steps and 93% *ee*.

Based on the reaction outcomes and the observed stereochemistry of the Michael adducts, a possible reaction mechanism is proposed for the Michael addition of nitromethane **2a** to β,β-disubstituted α,β-unsaturated aldehydes **1** catalyzed by the nonsilyl bicyclic secondary amine organocatalyst **3a**, as shown in Scheme 5. Accordingly, catalyst **3a** condenses with the β,β-disubstituted α,β-unsaturated aldehyde **1** to form the corresponding *E*-iminium ion intermediate **A**. The nucleophilic nitromethide ion, generated from nitromethane **2a**, then



Scheme 4 Concise asymmetric synthesis of methsuximide **9a**.



Scheme 5 Proposed reaction mechanism for the Michael addition of nitromethane **2a** to β,β-disubstituted α,β-unsaturated aldehydes **1** catalyzed by **3a**.

attacks the β-position of the iminium ion **B** from the face opposite to the chiral bulky substituent of the catalyst, leading to the formation of the enamine intermediate **C**. Upon protonation, the enamine intermediate **C** forms the iminium intermediate **D**, which undergoes hydrolysis to yield the Michael adduct **5** along with the regeneration of catalyst **3a.**

Conclusions

In summary, the nonsilyl bicyclic secondary amine organocatalysts **3a–3c** were investigated for the enantioselective Michael addition of nitromethane **2a** to β-methyl cinnamaldehyde **1a**. A broad range of β,β-disubstituted α,β-unsaturated aldehydes (**1a–1s**) were evaluated under the optimized reaction conditions, affording the corresponding products **4a–4s** bearing all-carbon quaternary stereocenters in 40–69% yields and 58–95% ees. Substrate **1t**, bearing an ester group at the β-position, was successfully converted to the corresponding Michael adduct **5t** in 62% yield and 93% ee. Additionally, the use of nitropropane **2b** as the nucleophile afforded product **4u** in 29% yield with 1.4 : 1 dr and 83% ee. A scale-up reaction was successfully performed at the 5.1 mmol scale using β-methyl cinnamaldehyde **1a**, delivering alcohol **4a** in 66% yield and 95% ee. Furthermore, the synthetic utility of this methodology was exemplified through a concise asymmetric synthesis of methsuximide, an anticonvulsant drug, starting from β-methyl cinnamaldehyde **1a**. Based on the stereochemical outcomes of the Michael adducts, a possible reaction mechanism has been proposed. This study is expected to stimulate further exploration on the use of nonsilyl bicyclic secondary amine organocatalysts for enantioselective Michael addition of various nucleophiles to α,β-unsaturated aldehydes.

Data availability

Data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

1 (*a*) K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191; (*b*) E. A. Peterson and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 11943–11948; (*c*) M. Büschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal and L. E. Overman, *Angew. Chem., Int. Ed.*, 2016, **55**, 4156–4186; (*d*) Y. Jia, K. Zhang, L.-Q. Lu, Y. Cheng and W.-J. Xiao, *ACS Catal.*, 2024, **14**, 13550–13556; (*e*) A. Y. Hong and B. M. Stoltz, *Eur. J. Org. Chem.*, 2013, 2745–2759; (*f*) S. Goswami, K. Harada, M. F. El-Mansy, R. Lingampally and R. G. Carter, *Angew. Chem., Int. Ed.*, 2018, **57**, 9117–9121; (*g*) T. S. Silva and F. Coelho, *Beilstein J. Org. Chem.*, 2021, **17**, 1565–1590; (*h*) X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang,

F. Zhou and J. Zhou, *Chem. Rev.*, 2016, **116**, 7330–7396; (*i*) T. Ema, Y. Oue, K. Akihara, Y. Miyazaki and T. Sakai, *Org. Lett.*, 2009, **11**, 4866–4869; (*j*) M. Tanaka, M. Imai, M. Fujio, E. Sakamoto, M. Takahashi, Y. Eto-Kato, X. M. Wu, K. Funakoshi, K. Sakai and H. Suemune, *J. Org. Chem.*, 2000, **65**, 5806–5816.

2 (*a*) C. Li, S. S. Ragab, G. Liu and W. Tang, *Nat. Prod. Rep.*, 2020, **37**, 276–292; (*b*) Y. Liu, S.-J. Han, W.-B. Liu and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740–751; (*c*) Z. Wang, *Org. Chem. Front.*, 2020, **7**, 3815–3841; (*d*) T. Ling and F. Rivas, *Tetrahedron*, 2016, **72**, 6729–6777; (*e*) R. Long, J. Huang, J. Gong and Z. Yang, *Nat. Prod. Rep.*, 2015, **32**, 1584–1601; (*f*) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil and B. M. Stoltz, *Nat. Chem.*, 2012, **4**, 130–133; (*g*) S.-J. Han, F. Vogt, S. Krishnan, J. A. May, M. Gatti, S. C. Virgil and B. M. Stoltz, *Org. Lett.*, 2014, **16**, 3316–3319; (*h*) R. M. Lemieux and A. I. Meyers, *J. Am. Chem. Soc.*, 1998, **120**, 5453–5457; (*i*) J. Deng, S. Zhou, W. Zhang, J. Li, R. Li and A. Li, *J. Am. Chem. Soc.*, 2014, **136**, 8185–8188; (*j*) R. Long, J. Huang, W. Shao, S. Liu, Y. Lan, J. Gong and Z. Yang, *Nat. Commun.*, 2014, **5**, 5707.

3 (*a*) A. G. Csakÿ, G. de la Herrán and M. C. Murcia, *Chem. Soc. Rev.*, 2010, **39**, 4080–4102; (*b*) C. Hawner and A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295–7306; (*c*) E. Fillion and A. Wilsily, *J. Am. Chem. Soc.*, 2006, **128**, 2774–2775; (*d*) A. Wilsily and E. Fillion, *Org. Lett.*, 2008, **10**, 2801–2804; (*e*) Y. Hamashima, D. Hotta and M. Sodeoka, *J. Am. Chem. Soc.*, 2002, **124**, 11240–11241; (*f*) C. Hawner, D. Muller, L. Gremaud, A. Felouat, S. Woodward and A. Alexakis, *Angew. Chem., Int. Ed.*, 2010, **49**, 7769–7772; (*g*) K. Endo, D. Hamada, S. Yakeishi and T. Shibata, *Angew. Chem., Int. Ed.*, 2013, **52**, 606–610; (*h*) R. Shintani, Y. Tstsumi, M. Nagaosa, T. Nishimura and T. Hayashi, *J. Am. Chem. Soc.*, 2009, **131**, 13588–13589.

4 (*a*) K. Akagawa and K. Kudo, *Angew. Chem., Int. Ed.*, 2012, **51**, 12786–12789; (*b*) J.-M. Tian, Y.-H. Yuan, Y.-Q. Tu, F.-M. Zhang, X.-B. Zhang, S.-H. Zhang, S.-H. Wang and X.-M. Zhang, *Chem. Commun.*, 2015, **51**, 9979–9982; (*c*) Y. Hayashi, Y. Kawamoto, M. Honda, D. Okamura, S. Umemiya, Y. Noguchi, T. Mukaiyama and I. Sato, *Chem. – Eur. J.*, 2014, **20**, 12072–12082; (*d*) T. Mukaiyama, K. Ogata, I. Sato and Y. Hayashi, *Chem. – Eur. J.*, 2014, **20**, 13583–13588.

5 (*a*) M. H. Haindl, M. B. Schmid, K. Zeitler and R. M. Gschwind, *RSC Adv.*, 2012, **2**, 5941–5943; (*b*) X. Companyó and J. Burés, *J. Am. Chem. Soc.*, 2017, **139**, 8432–8435; (*c*) G. Hutchinson, C. Alamillo-Ferrer and J. Burés, *J. Am. Chem. Soc.*, 2021, **143**, 6805–6809.

6 R. Kumar, V. Maurya, A. Avinash and C. Appayee, *J. Org. Chem.*, 2024, **89**, 8586–8600.

7 For the synthesis of methsuximide, see: (*a*) P.-W. Xu and Z.-X. Huang, *Nat. Chem.*, 2021, **13**, 634–642; (*b*) Y. Kuroiwa and M. Tamura, *Adv. Synth. Catal.*, 2024, **366**, 1996–2002; (*c*) J. Li, J. Wei, B. Zhu, T. Wang and N. Jiao, *Chem. Sci.*, 2019, **10**, 9099–9103 For the biological activity of methsuximide, see: (*d*) J. Mifsud, J. S. Millership, P. S. Collier, R. Morrow, J. T. G. Hamilton and W. C. McRoberts, *Biopharm. Drug Dispos.*, 2001, **22**, 129–136; (*e*) R. J. Porter, J. K. Penry, J. R. Lacy, M. E. Newmark and H. J. Kupferberg, *Neurology*, 1979, **29**, 1509–1513.

8 Under the optimized reaction conditions, product **4p** was obtained in 80% yield and 27% ee after 16 h.