Article

Diastereo- and Enantioselective Synthesis of Structurally diverse Succinate, Butyrolactone, Trifluoromethyl Derivatives by Iridium Catalyzed Hydrogenation of Tetrasubstituted Olefins

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Diastereo- and Enantioselective Synthesis of Structurally diverse Succinate, Butyrolactone, Trifluoromethyl Derivatives by Iridium Catalyzed Hydrogenation of Tetrasubstituted Olefins

Sutthichat Kerdphon,[‡a] *Sudipta Ponra,*[‡a] *Jianping Yang,*[‡a] *Haibo Wu,*[a] *Lars Eriksson*[b] *and Pher G. Andersson**[a][c]

[a]Department of Organic Chemistry, Stockholm University, Arrhenius Laboratory, 106 91, Stockholm, Sweden; E-mail: pher.andersson@su.se

[b]Department of Materials and Environmental Chemistry, Stockholm University, Svante Arrhenius väg16C, SE-10691, Stockholm, Sweden

[c]School of Chemistry and Physics, University of KwaZulu-Natal, Durban, South Africa.

Abstract: A highly efficient iridium N,P-ligand catalyzed asymmetric hydrogenation of functionalized tetrasubstituted olefins lacking a directing group, has been developed. Various structural diverse chiral succinate derivatives were obtained in high yields and excellent enantio- and diastereoselectivities (up to 99% *ee*) using 0.5 - 1.0 mol% catalyst loadings. This stereoselective reaction is applicable for synthesis of chiral acyclic molecules (up to >99% *ee*) having two contiguous stereogenic centers and is compatible with various aromatic, aliphatic and heterocyclic systems, a variety of functional groups of different electronic nature. Furthermore, this asymmetric protocol allows a short enantioselective route to the butyrolactone building block, an intermediate in the synthesis of anticancer agent BMS-871 and pharmaceuticals (2*S*)-(-)-Verapamil, (2*S*)-(-)-Gallopamil.

Keywords: tetrasubstituted olefin, asymmetric hydrogenation, iridium catalysis, enantioselective, diastereoselective.

INTRODUCTION

Succinic acid derivatives are important building blocks in both organic and medicinal chemistry. For instance, these derivatives are employed as inhibitors of renin[1] and matrix metalloproteinases[2]. Moreover, succinates are used mainly as non-phthalate plasticizers[3] in the cosmetic industry[4] and agricultural chemistry, and in material science as monomers for polymers and dendrimers.[5] Substituted butyrolactones are also

common structural motifs in a wide range of complex natural products (Figure 1. A) and serve as chiral building blocks in the synthesis of biologically active compounds (Figure 1. B).[6] Consequently, numerous methods and strategies have been developed for the synthesis of succinate derivatives.[7, 8] However, efficient catalytic and enantioselective synthesis[8] of these important building blocks containing two contiguous stereocenters are unexplored and the general catalytic asymmetric synthesis of these derivatives still presents a major challenge.[8f]

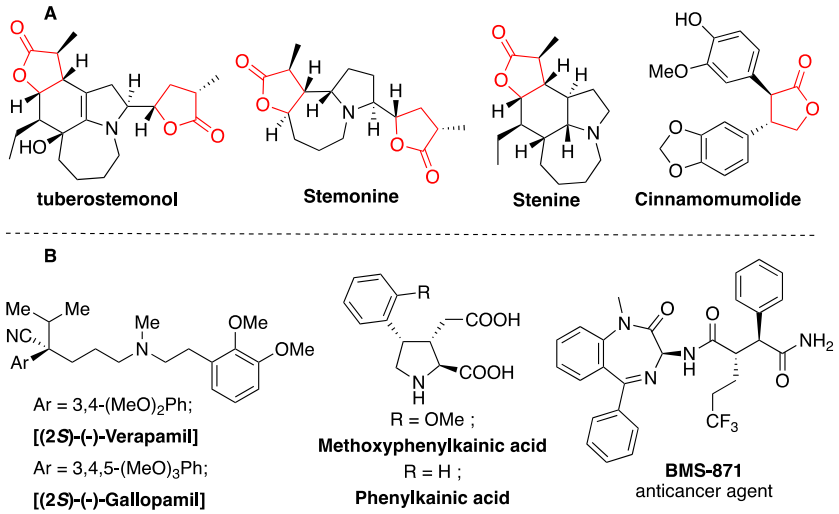
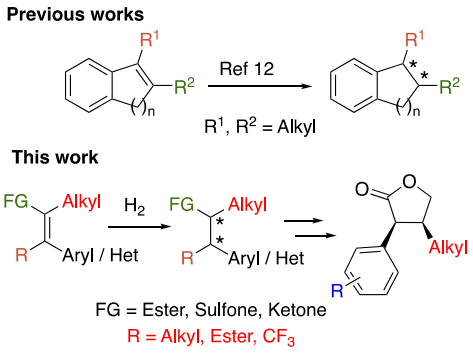


Figure 1. A. Natural products containing butyrolactone motif. **B**. Bioactive molecules derived from butyrolactone or chiral succinate compounds.

Asymmetric hydrogenation of tetrasubstituted olefins (AHTOs) possesses tremendous potential in stereoselective synthesis since it enables the introduction of two vicinal stereocenters in one single step. Despite this, progress in this area has grown at a relaxed pace,[9] partly because of the difficulties in differentiation of the prochiral faces of a fully substituted olefin, and partly the steric hindrance of the four different

substituents, which results in a slow rate of hydrogenation of these substrates in comparison to the di- and tri-substituted olefins. Highly enantioselective hydrogenation of olefins lacking a coordinative group is even more difficult as the coordinating group assists in the transfer of the chiral information from the catalyst to the product.[10] The limited number of reports in literature on the AHTOs without a coordinating group compared to the AHTOs with a coordinating group, further proves these difficulties.[9a] To date, the catalytic system that has been reported was successful for only a few special types of substrates. Also, each class of olefins requires a special catalytic system.[11] Examples of AHTOs a lacking coordinating group is still limited[12] for cyclic olefins[12a-e, 12g, 12h] and for acyclic olefins are very rare (Scheme 1).[12c, 12f-h] The reported methods require either high catalyst loadings,[12a-e] a mixture of catalysts,[12e] or sophisticated reaction conditions.[12e] Furthermore, there are only a few methods available for the hydrogenation of tetrasubstituted non-chelating olefins having functional groups that are able to create useful building blocks for further synthesis.[12e] Thus, development of a catalyst having a wide substrate scope for AHTOs to access versatile building blocks is still a very challenging task in asymmetric hydrogenation. Here we report our work to develop a general, simple, and efficient atom-economical protocol for the highly enantioselective synthesis of different chiral building blocks containing two stereogenic centers.

Scheme 1. Asymmetric hydrogenation of tetrasubstituted olefins without coordinating group.



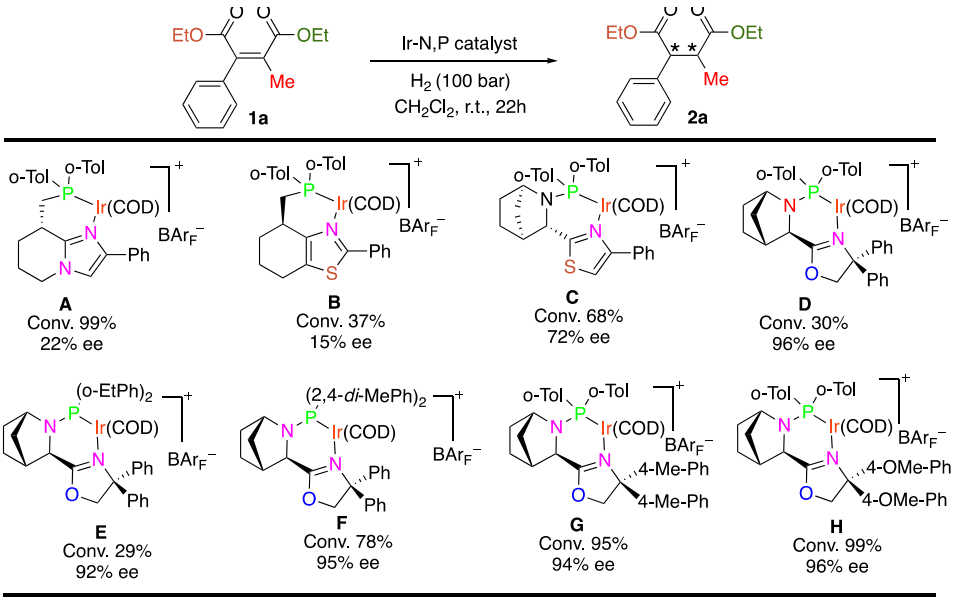
RESULTS AND DISCUSSION

Initially, (*Z*)-diethyl 2-methyl-3-phenylmaleate **1a** was chosen as test substrate for asymmetric hydrogenation by using iridium-N,P complex as the catalyst. Normally, acyclic tetra-substituted olefins containing non-chelating groups[12a] specially two ester groups[12f] are notoriously difficult substrates since these olefins are both electron deficient *and* lack chelating groups that would facilitate binding to the catalyst as well as discrimination between the two enantiotopic faces.

It was found that olefin **1a** could be hydrogenated in good yield using imidazole N,P-Ir complex **A** but with poor enantioselectivity (Table 1). Subsequently, several chiral iridium Crabtree-type catalysts having thiazole and oxazoline N,P-ligands were evaluated using 0.5 mol% of catalyst loading. The catalyst containing a thiazole ligand **B** resulted in poor conversion and enantioselectivity. Catalyst **C**, containing a bicyclic

thiazole led to an improved enantioselectivity (72%). Interestingly, the bulkier iridium N, P-catalyst **D** having a di-phenyl substituted oxazoline led to a much higher enantiomeric excess, 96% *ee*. The promising result obtained for catalyst **D** prompted us to further modify the catalyst structure by varying the substituents on the phosphine and phenyl of the oxazoline ring. Changing the *ortho*-methyl group to an *ortho*-ethyl substituent on phosphine for catalyst **E** did not improve the efficiency nor the selectivity of the hydrogenation reaction. Catalyst **F** with the more electron-rich di(2,4-dimethylphenyl)-phosphine group, resulted in a higher reactivity (78% conversion, 95% *ee*) compared to catalyst **E**. The introduction of electron-rich substituents on the two phenyl groups on the oxazoline ring, (4-Me-Ph and 4-OMe-Ph, catalyst **G** and **H**), further improved the yield of hydrogenation products. Amongst the newly developed catalysts (Table 1), the highest reactivity for substrate **1a** was recorded with catalyst **H** which afforded 96% *ee* with full conversion using a catalyst loading of only 0.5 mol%.

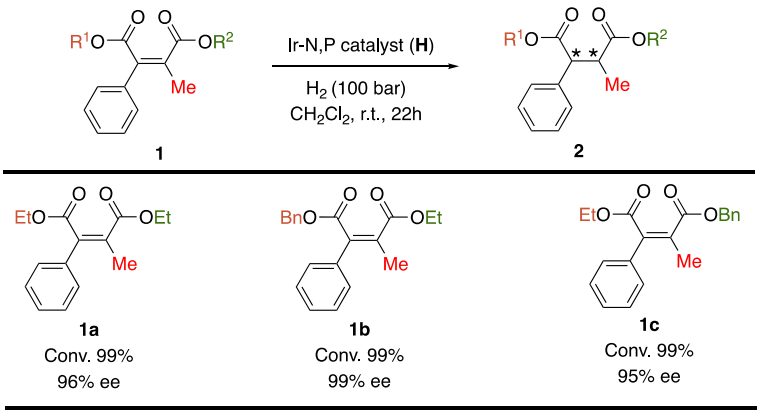
Table 1. Evaluation of N,P-iridium catalysts in the asymmetric hydrogenation of 1a[a]



[a]Reaction conditions: 0.05 mmol substrate, 0.5 mol% catalyst, 0.5 mL CH_2Cl_2. Conversions were determined by ^{1}H-NMR spectroscopy. Enantiomeric excess determined by HPLC and SFC-HPLC analysis using a chiral stationary phase.

Having identified suitable catalysts and establishing the optimized conditions, different ester groups were screened in the hydrogenation (Table 2). The possibility to have two ester groups possessing orthogonal reactivity would enable one to differentiate between them and render them more useful in further synthesis. Ester groups had proved to have significant influence on the reactivity and on enantioselectivities (see Supporting Information for details) and changing from the diethyl ester to benzyl-ethyl ester **1b** was found to be best both in terms of enantioselectivity (99% *ee*) and conversion (99%). The other benzyl-ethyl ester **1c** also provides high conversion (99%) but in slightly lower *ee* (95%). Based on the high reactivity and enantioselectivity for substrate **1b** it was chosen as the suitable substrate class for further studies on the efficacy of this reaction.

Table 2. Optimization of reaction conditions for the hydrogenation of tetrasubstituted maleate olefins[a]

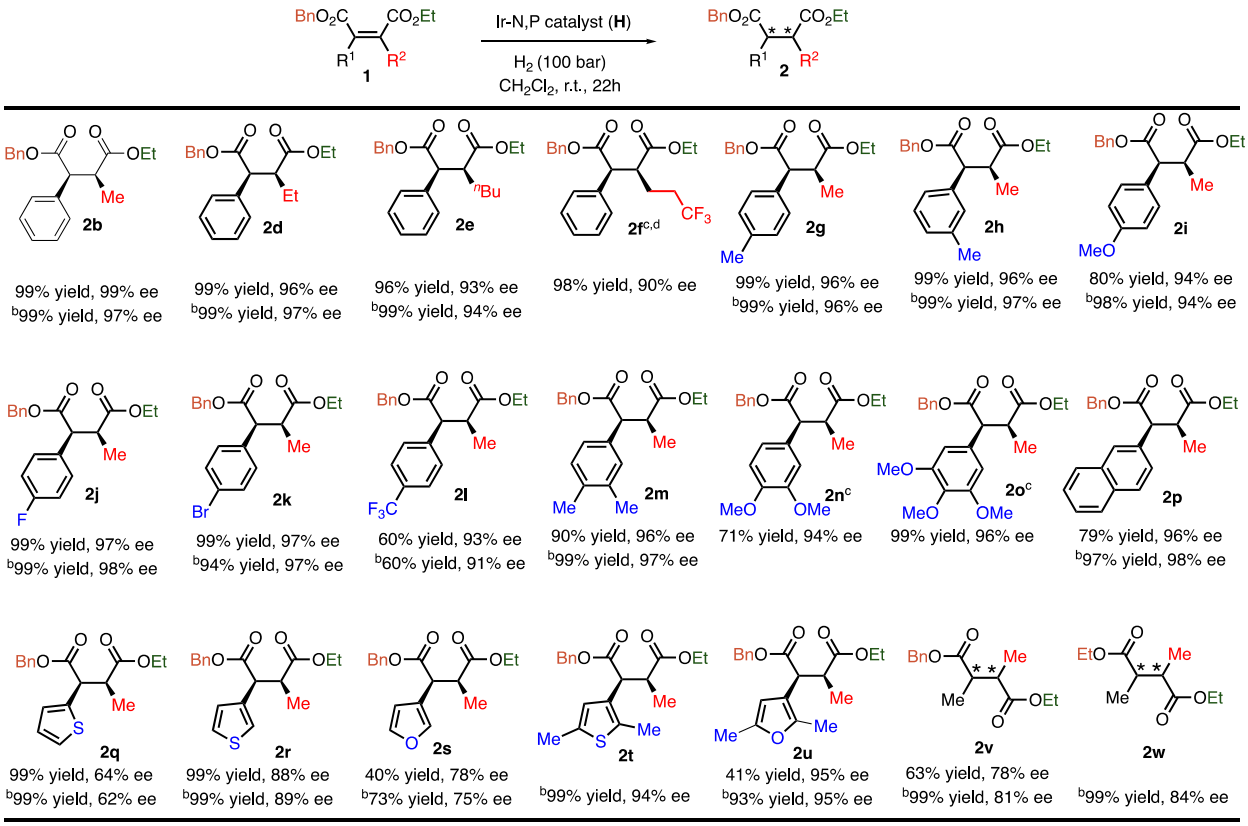


[a]0.5 mol% catalyst **H**, 0.5 mL CH_2Cl_2. Conversion determined by ^{1}H-NMR spectroscopy. Enantiomeric excess determined by HPLC and SFC-HPLC analysis using a chiral stationary phase.

A series of di-ester derivatives were successfully hydrogenated using newly synthesized catalyst **H** to give the products in excellent yield, complete diastereoselectivity and high to excellent enantioselectivities (Table 3). First, substrates bearing different alkyl groups, ranging from short to longer aliphatic chain substituents on the olefin (**1b**-**1f**), were evaluated and all the substrates were hydrogenated efficiently (**2b**-**2f**) in excellent yield (96-99%) and enantioselectivities (90-99% *ee*). The maleate derivatives bearing either electron-donating or electron-withdrawing substituents gave good to excellent isolated yield (60-99%) with excellent enantioselectivity (91-98% *ee*). The reaction also allowed several electron-donating group (Me or OMe) on the aromatic ring and smoothly afforded **2m**-**2o** in high yields and enantiomeric excess. The maleate **1p** with the bulkier 2-naphthyl substituent gave

the product **2p** in good yield and excellent enantioselectivity of 98%. A number of heterocyclic compounds with different substitutions were also evaluated in the hydrogenation using both catalysts **H** and **D** with promising results. Interestingly, challenging substrates having aliphatic substituents (**1v** and **1w**) were hydrogenated (*E*-isomer) in high levels of reactivity (99% yield), and good enantioselectivity (81% and 84% *ee* respectively).

Table 3. Asymmetric hydrogenation of tetrasubstituted maleate olefins.

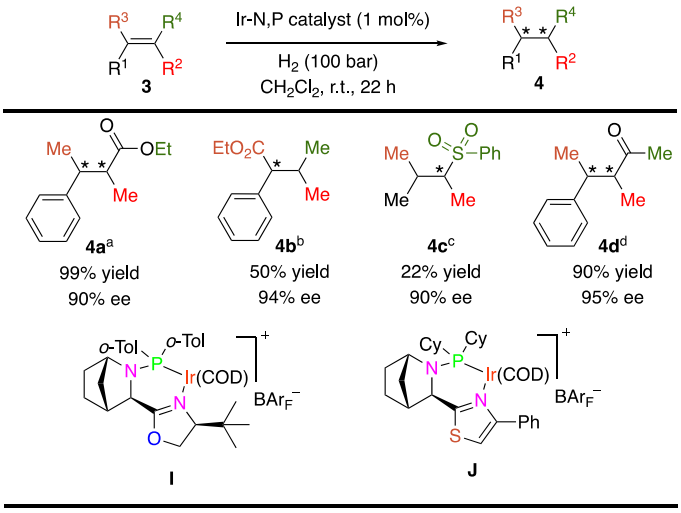


[a]Reaction conditions: 0.1 mmol substrate, 0.5 mol% catalyst **H**, 0.5 mL CH_2Cl_2. [b]Reaction conditions: 0.2 mmol substrate, 1.0 mol% catalyst **D**, 2.0 mL Benzene. [c]2.0 mol% catalyst **H**. [d]130 bar H_2. Enantiomeric excess was determined by SFC-HPLC analysis using a

chiral stationary phase. All yields are isolated yield. Conversions were determined by ^{1}H-NMR spectroscopy.

To investigate the substrate scope of this atom-economical process in addition to the di-esters, several mono-functionalized olefins were also investigated (Table 4). Catalyst **I** was found to hydrogenate α, β-unsaturated ester **3a** to give **4a** in high yield (99%) and excellent 90% *ee*. For ester **3b** catalyst **D** provides best result in 50% yield with enantioselectivity of 94% *ee*. Similarly, *α, β*-unsaturated sulfone **3c** was successfully hydrogenated using catalyst **J** with high level of enantioselectivity (90% *ee*) but in only 22% isolated yield. Chemoselective hydrogenation of the olefin for *α, β*-unsaturated ketone **3d** was also successful under optimized reaction condition in high 90% yield with excellent 95% *ee*.

Table 4. Asymmetric hydrogenation of mono-functionalized tetrasubstituted olefins.

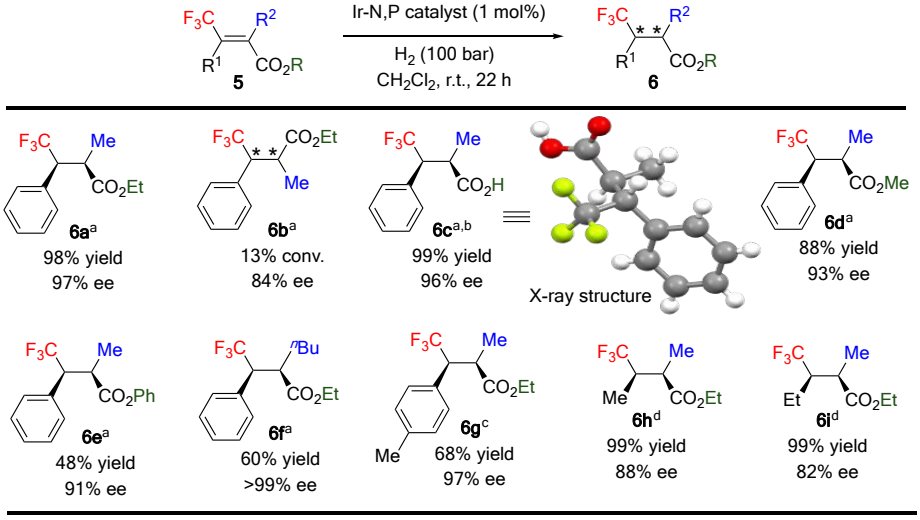


Reaction conditions: 0.05 mmol substrate, 1.0 mol% catalyst, 0.5 mL CH_2Cl_2. The conversions were determined by ^{1}H-NMR spectroscopy. [a]Catalyst **I**, [b]catalyst **D**, [c]catalyst **J**, [d]catalyst **D** in benzene. Enantiomeric excess determined by SFC-HPLC analysis using a chiral stationary phase and GC analysis using a chiral stationary phase.

The trifluoromethyl group (-CF_3) by virtue of its special properties provides a pivotal role in pharmaceuticals, agrochemicals and material chemistry such as liquid crystals.[13] To further study the boundaries of this highly stereoselective hydrogenation process, we also evaluated a number of tetrasubstituted trifluoromethyl olefins that results in synthetically useful chiral trifluoromethyl molecules with two contiguous stereogenic centers (Table 5). Optimization using (*E*)-ethyl trifluoromethyl-3-phenylbut-2-enoate **5a** as the standard substrate proved that catalyst **B** is most suitable (see Supporting Information for optimization details). Both *E*- and *Z*-isomer of trifluoromethyl containing α, β-unsaturated ethyl ester could be hydrogenated in good to excellent enantioselectivity. *E*-isomer **5a** provides 98% yield and 97% *ee*, whereas the opposite *Z*-isomer **5b** resulted in product **6b** with 84% *ee* albeit in only 13% conversion. The established catalytic system proved effective for a large variety of different esters (**5c**-**5f**) and produced the desired products in good to excellent yield (48-99%) and high enantioselectivities (91->99% *ee*). Weak electron-donating (Me) substituent on the aromatic ring **5g** was well tolerated and the best result of 68% yield and 97% *ee* was obtained by using catalyst **D**. Another significant advantage of the reaction is that substrates (**5h** and **5i**) having aliphatic substituents can be hydrogenated in high yields (99%) and good levels of stereoselectivity (88% *ee* and 82% *ee* respectively). The fruitful examples of this reported reaction conditions to synthesize chiral trifluoromethyl

molecules with two contiguous stereogenic centers in mostly good to excellent yield, with exceptional diastereoselectivities (>99%) and enantioselectivities (up to >99%) again underlines that this catalytic system is very general for tetrasubstituted trifluoromethyl-olefins.

Table 5. Asymmetric hydrogenation of CF_3 containing tetrasubstituted olefins.

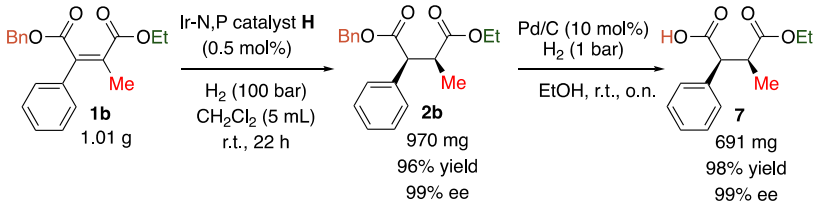


Reaction conditions: 0.05 mmol substrate, 1.0 mol% catalyst, 0.5 mL CH_2Cl_2. [a]1.0 mol% catalyst **B**. [b]Corresponding ^{t}Bu ester was used as starting material for compound **6c** and used for absolute configuration determination (CCDC 1907708). [c]1.0 Mol% catalyst **D**. [d]1.0 Mol% catalyst **C**, The conversion was determined by ^{1}H-NMR spectroscopy. Enantiomeric excess determined by SFC-HPLC analysis using a chiral stationary phase and GC analysis using a chiral stationary phase.

The practicality of this Ir-catalyzed hydrogenation reaction was confirmed for the large scale production of chiral succinate derivative. A gram-scale set-up using for 1.0 g of starting material **1b**, 0.5 mol% of catalyst **H** produced the desired compound **2b** in excellent 96% yield and >99% *ee*. Hydrogenolysis using Pd-C in EtOH under 1 bar

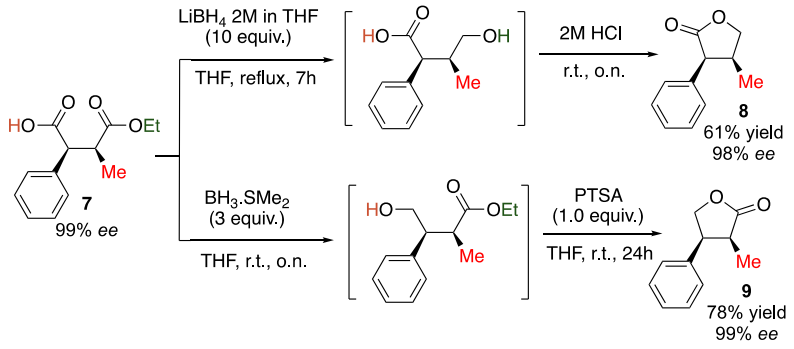
hydrogen pressure resulted in the desired 4-ethoxy-3-methyl-4-oxo-2-phenylbutanoic acid **7** in 98% isolated yield with 99% *ee* (Scheme 2).

Scheme 2. Gram-scale production of chiral succinate derivative



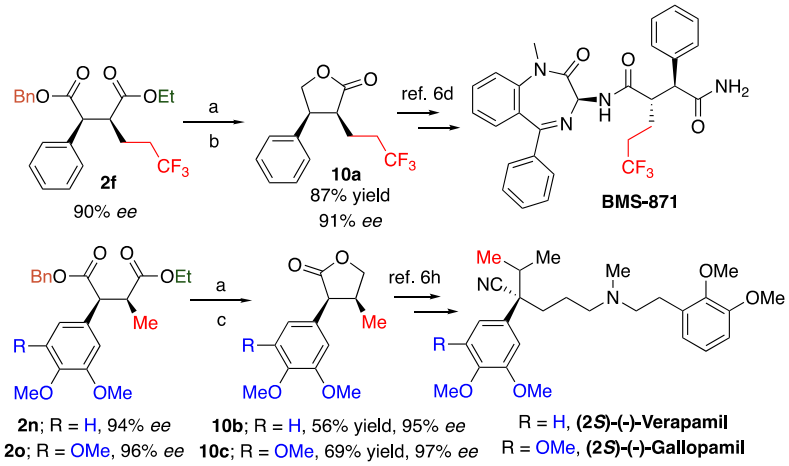
Having two different ester groups in the hydrogenated product **2b** is very useful since they can be easily differentiated by an orthogonal deprotection (Scheme 3). Lactone **8** was prepared *via* selective reduction of the ethyl ester group of **7** using $LiBH_4$ to generate 4-hydroxy-3-methyl-2-phenylbutanoic acid. Under acidic conditions this intermediate cyclized to produce lactone **8** in 61% isolated yield in 98% *ee*. The regio-isomeric *cis*-lactone **9** was prepared in 78% isolated yield with excellent 99% *ee via* a divergent route using a one-pot, chemo-selective reduction of the carboxyl acid group using $BH_3.SMe_2$ followed by cyclization in the presence of PTSA. Both the selective reduction and cyclization reaction proceeds with excellent preservation of stereochemistry.

Scheme 3. Derivatization of enantiomeric compounds from hydrogenation reaction *via* chemoselective reduction.



To demonstrate the synthetic utility of the developed methodology, the reaction was successfully applied for the formal synthesis of anticancer agent BMS-871 and calcium channel-blockers Verapamil and Gallopamil (Scheme 4). Hydrogenated product **2f** was efficiently converted to the butyrolactone **10a** in 87% yield and 91% *ee* using the two-step strategy of hydrogenolysis and selective reduction of the carboxylic acid, followed by cyclization as discussed in the reaction sequence of Scheme 3. Similarly, succinate derivatives **2n** and **2o** were converted to corresponding butyrolactones **10b** or **10c** in good yields and excellent *ee*. Butyrolactone **10a**, **10b** or **10c** are precursors for the formal synthesis of aforesaid bioactive molecules.[6d, h]

Scheme 4. Enantioselective formal synthesis of BMS-871, (2*S*)-(-)-Verapamil, (2*S*)-(-)-Gallopamil.



Reaction condition (a) H_2 (1 bar), Pd/C (10 mol%), EtOH, r.t., o.n. (b) $BH_3.SMe_2$ (3 equiv.), THF, r.t., o.n.; PTSA (1.0 equiv.), THF, r.t., 24h. (c) $LiBH_4$ 2M in THF (10 equiv.), THF, reflux, 7h.

CONCLUSION

A variety of tetrasubstituted, acyclic olefins have been successfully evaluated in asymmetric hydrogenation using catalytic amounts of new N, P-iridium catalysts (0.5-1 mol%). Two adjacent stereogenic centers were introduced during the asymmetric hydrogenation with complete diastereoselectivity and excellent enantiomeric excess (up to >99%). The enantiomerically enriched succinate derivatives were converted to chiral building block butyrolactones by simple and easy reaction condition *via* hydrogenolysis followed by chemoselective reduction and lactonization, respectively. The feasibility and the utility of this protocol were finally confirmed by the gram-scale synthesis of useful building blocks and by the formal stereoselective synthesis of anticancer agent BMS-871 and pharmaceuticals (2*S*)-(-)-Verapamil, (2*S*)-(-)-Gallopamil.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, crystallography reports, and analytical data (PDF)

Crystallographic data for **6c** (CIF)

AUTHOR INFORMATION

Corresponding Author

*Pher.Andersson@su.se

Author Contributions

‡ S.K., S.P. and J.Y. contributed equally.

Notes

The authors declare no competing financial interest.

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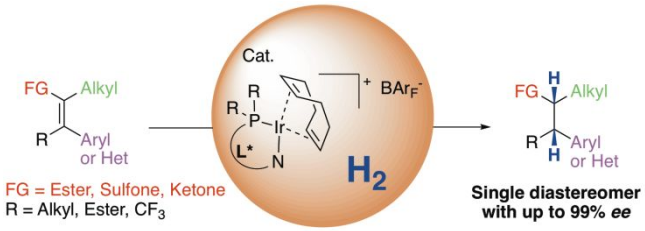
SYNOPSIS



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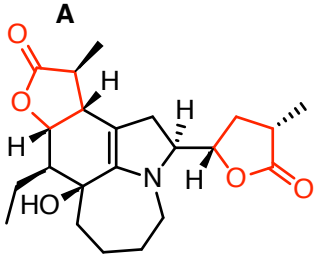

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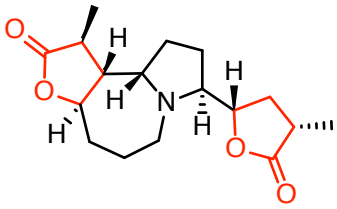

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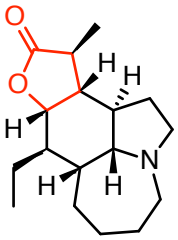

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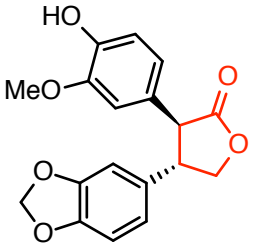
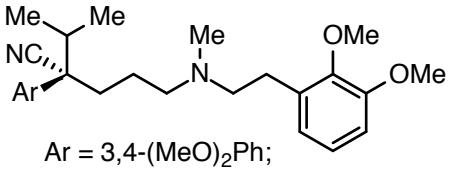


Cinnamomumolide

B



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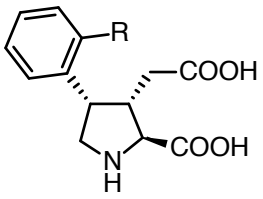
[(2*S*)-(-)-Verapamil]

Ar = 3,4,5-$(MeO)_3$Ph;

[(2*S*)-(-)-Gallopamil]

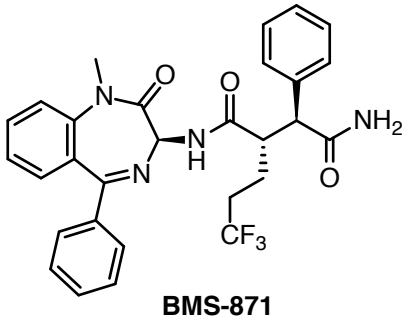


R = OMe ;

Methoxyphenylkainic acid

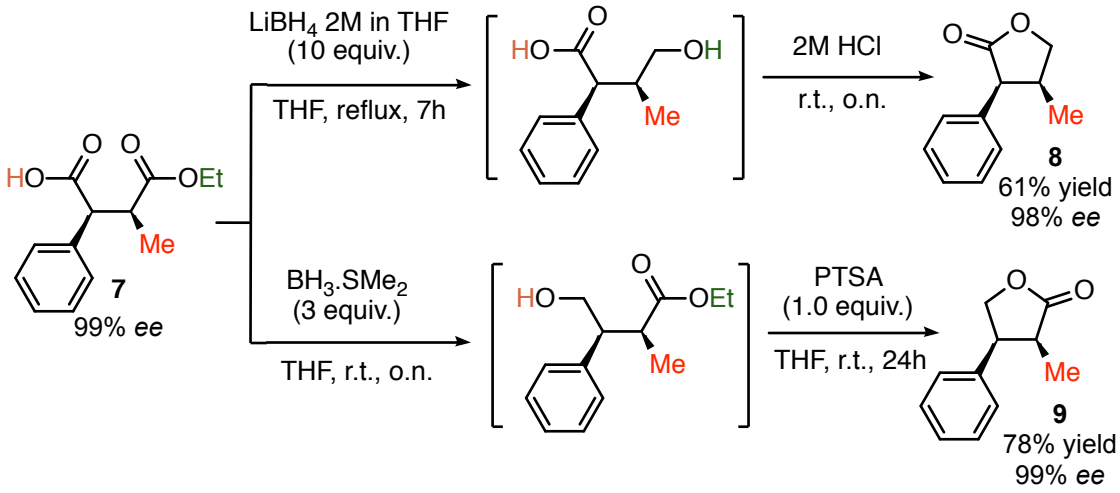
R = H ;

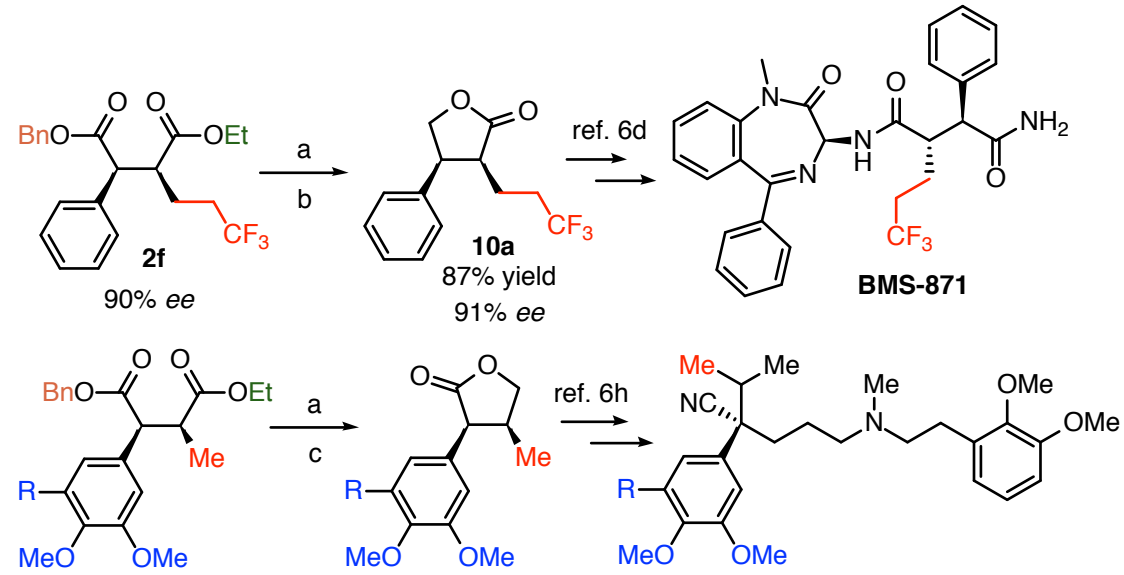
Phenylkainic acid



BMS-871

anticancer agent


LiBH4 2M in THF
(10 equiv.)
THF, reflux, 7h
2M HCl
r.t., o.n.
8
61% yield
98% ee
7
99% ee
BH3.SMe2
(3 equiv.)
THF, r.t., o.n.
PTSA
(1.0 equiv.)
THF, r.t., 24h
9
78% yield
99% ee


BnO
OEt
CF3
2f
90% ee
a
b
10a
87% yield
91% ee
ref. 6d
NH2
BMS-871
Me
R
MeO
OMe
c
2n; R = H, 94% ee
2o; R = OMe, 96% ee
10b; R = H, 56% yield, 95% ee
10c; R = OMe, 69% yield, 97% ee
ref. 6h
NC
R = H, (2S)-(-)-Verapamil
R = OMe, (2S)-(-)-Gallopamil

Diastereo- and Enantioselective Synthesis of Structurally diverse Succinate, Butyrolactone, Trifluoromethyl Derivatives by Iridium Catalyzed Hydrogenation of Tetrasubstituted Olefins

Sutthichat Kerdphon,[‡][a] Sudipta Ponra,[‡][a] Jianping Yang,[‡][a] Haibo Wu,[a] Lars Eriksson[b] and Pher G. Andersson[a][c]*

[a] Department of Organic Chemistry, Stockholm University, Arrhenius Laboratory, 106 91, Stockholm, Sweden; E-mail: pher.andersson@su.se
[b] Department of Materials and Environmental Chemistry, Stockholm University, Svante Arrhenius väg16C, SE-10691, Stockholm, Sweden
[c] School of Chemistry and Physics, University of KwaZulu-Natal, Durban, South Africa.