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A New Iron(III)–Salen Catalyst for Enantioselective Conia-ene Carbocyclization

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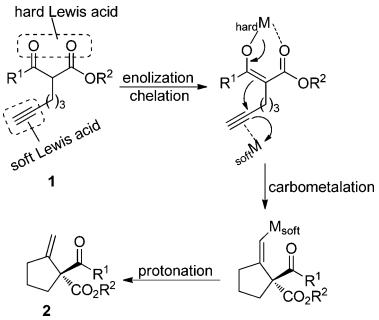
Supporting Information

ABSTRACT: A chiral iron(III)–salen complex based on a *cis*-2,5-diaminobicyclo[2.2.2]octane scaffold catalyzes asymmetric Conia-ene-type cyclization of α-functionalized ketones containing an unactivated terminal alkyne and produces an *exo*-methylenecycloalkane possessing a stereodefined quaternary center.

Intramolecular addition of enols and enolates to unactivated alkenes and alkynes is a powerful method for obtaining carbocycles bearing multiple substituents.[1] The Conia-ene synthesis exemplifies this concept even though its early thermal version required high temperatures that were incompatible with sensitive functionality.[2] Advances in transition-metal catalysis made the Conia-ene synthesis a more practical method of carbocyclization,[3] but it took three decades from the reaction's inception to develop an enantioselective version of the process. Recent studies by Toste,[4] Dixon,[5] and Shibasaki[6] have addressed this problem and have led to a working hypothesis for effecting asymmetric cyclization of α-pentynyl-β-dicarbonyl structures **1** in which a dual catalyst system consisting of a hard Lewis acid to promote enolization and a soft Lewis acid, usually a transition metal, to activate the alkyne is the key feature (Scheme 1). The

Scheme 1. General Mechanism of Carbocyclization of Alkynyl β-Keto Esters Catalyzed by a Combination of Hard and Soft Lewis Acids



Toste–Dixon–Shibasaki methodology represents a valuable technique for generating a carbocycle bearing malleable functional groups and a stereogenic quaternary carbon, but it has been applied only to the synthesis of chiral cyclopentanes **2** and frameworks containing this ring.

In a project designed to enlarge the scope of enantioselective metallo–ene carbocyclization, we have examined several chiral metal–salen systems as catalysts in which *cis*-2,5-diaminobicyclo[2.2.2]octane (**3**) forms the C_2-symmetric scaffold of the salen ligand.[7] Our previous studies with metal–salen complexes based on **3** found that they can be highly effective asymmetric catalysts for a variety of reactions,[8] and we reasoned that the catalytic principle expressed in Scheme 1 could be transferred to a system in which **3** sets the stage for stereogenesis.

Exploratory studies were conducted with β-keto ester **4** and were guided initially by a report that **4** in the presence of catalytic nickel acetylacetonate and ytterbium triflate gave cyclopentane **5**.[9] However, treatment of **4** with Ni(II)–salen complex **6**,[7] Cr(III) complex **7**, or Al(III) complex **8** (Figure 1) in the presence of

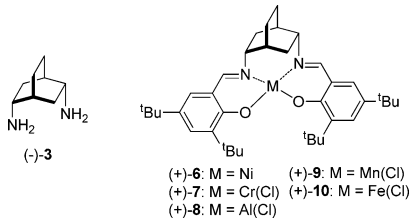


Figure 1. Diamine **3** and metal–salen complexes **6**–**10** based on a *cis*-2,5-diaminobicyclo[2.2.2]octane scaffold.

several rare-earth triflates as cocatalysts gave **5** in only modest yield with very low enantiomeric excess (ee) (Table 1, entries 1 and 2). On the other hand, Mn(III)– and Fe(III)–salen complexes **9** and **10** resulted in a marked increase in the yield of **5** even in the absence of a cocatalyst (entries 3 and 4).[10] The predominant enantiomer of **5** formed with these catalysts was found to have the *R* absolute configuration by comparison of its optical rotation with the literature value.[4] Although the enantioselectivity was still low with **9** and **10**, a study carried out with **10** in the presence of silver salts as additives (entries 5–8) revealed that further improvement in the yield of cyclization product **5** could be achieved, with silver trifluoroacetate and silver triflate showing the most promise.

In an effort to identify the active catalyst in these reactions, **10** was treated with an equimolar quantity of silver trifluoroacetate in dichloromethane, and after removal of insoluble silver chloride, iron–salen complex **11** was isolated as a brown amorphous solid (Scheme 2). This substance was used in subsequent experiments with **4**. Examination of solvent effects on the reaction of **4** in the presence of **11** showed a strong dependence of the product yield and reaction time on the solvent polarity, with dichloroethane (DCE) giving the best results (Table 2, entries 6 and 7). Unfortunately, the ee of **5** remained low.

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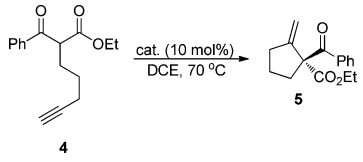
Table 1. Asymmetric Conia-ene Cyclization of β-Keto Ester 4 Catalyzed by Metal−Salen Complexes[a]



				product **5**	
entry	catalyst	additive	t [h]	yield [%][b]	ee [%][c]
1	(+)-**7**	–	30	42	12
2	(+)-**8**	–	52	29	7
3	(+)-**9**	–	30	67	29
4	(+)-**10**	–	14	69	38
5	(+)-**10**	AgOAc	21	65	42
6	(+)-**10**	$Ag(OCOCF_3)$	12	91	53
7	(+)-**10**	$AgBF_4$	15	82	34
8	(+)-**10**	AgOTf	12	94	39

[a]The reactions were carried out on a 0.25 mmol scale in a 0.0625 M solution of DCE using 10 mol % metal−salen complex and, for entries 5−8, 10 mol % additive. [b]Yields of isolated products. [c]Determined by HPLC using a Chiralcel OD column.

Scheme 2. Synthesis of Iron(III) Trifluoroacetate Complex (+)-11 from (+)-10

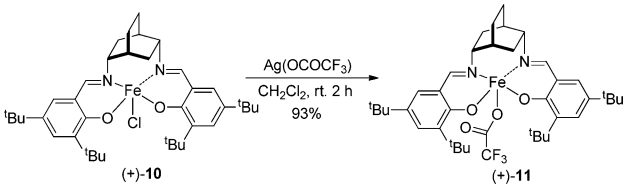
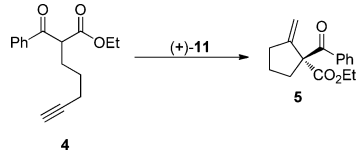


Table 2. Asymmetric Conia-ene Cyclization of β-Keto Ester 4 with Iron(III)−Salen Catalyst (+)-11: Effect of Catalyst Loading, Solvent, and Temperature[a]



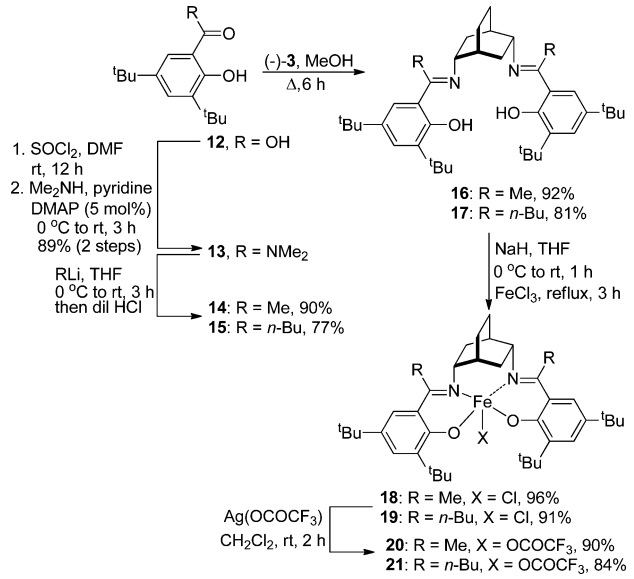
					product **5**	
entry	mol % (+)-**11**	solvent	T [°C]	t [h]	yield [%][b]	ee [%][c]
1	10	MeCN	70	56	39	10
2	10	PhMe	70	20	32	45
3	10	$CHCl_3$	60	16	91	49
4	10	dioxane	70	48	46	16
5	10	THF	66	48	51	12
6	10	DCE	70	12	91	57
7	20	DCE	70	9	95	59

[a]The reactions were carried out on a 0.25 mmol scale in a 0.0625 M solution. [b]Yields of isolated products. [c]Determined by HPLC using a Chiralcel OD column.

After considering options to improve the enantioselectivity in the Conia-ene cyclization of **4**, we decided to modify the salen ligand by increasing the steric bulk around the imine nitrogens of **11**. The rationale underlying this approach was drawn from transition-state models previously proposed for reactions involving metal−salen complexes based on **3**, where an aryl substituent attached to the imine function of the salen ligand obstructs approach to one face of the metal-bound reactant.[7,8] We reasoned that replacing the hydrogen at the imine carbons in **11** with an alkyl substituent would enhance the steric effect that steers attack by the alkyne toward the open face of the planar iron enolate formed with **4**.

The synthesis of our second-generation variant of **11** began with conversion of 2,4-di-*tert*-butylsalicylic acid (**12**) to the corresponding amide **13** (Scheme 3).[11] Reaction of **13** with

Scheme 3. Synthesis of Second-Generation Iron(III)−Salen Complexes (+)-20 and (+)-21



methyllithium and *n*-butyllithium gave ketones **14** and **15**, respectively, and condensation of these ketones in a 2:1 molar ratio with **3** furnished salen ligands **16** and **17** as yellow solids. Treatment of these imines with sodium hydride in THF and then with ferric chloride under reflux produced iron(III)−chlorosalen complexes **18** and **19**, which were advanced to the corresponding trifluoroacetates **20** and **21** by reaction with stoichiometric silver trifluoroacetate in dichloromethane.

Exposure of **4** to 5 mol % catalyst **20** in DCE at 70 °C produced **5** with promising enantioselectivity (Table 3, entry 1), and subsequent experiments with **21** increased this level of stereoselection (entries 2−6). The optimum reaction conditions were found to be 7.5 mol % catalyst **21** in chloroform at 50−60 °C (entries 5 and 6), parameters that gave **5** in 93−96% yield with 90−93% ee.

The conditions identified in entry 6 of Table 3 were then applied to a series of α-pentynyl ketones **23** bearing an electron-withdrawing group at the α-carbon. The results are shown in Table 4. In most cases, *exo*-methylenecyclopentanes **24**−**39** were formed in >90% yield with >90% ee. Further, it was found that α-hexynyl- and α-heptynyl-substituted β-keto esters undergo carbocyclization in the presence of iron−salen catalyst **21** to give *exo*-methylenecyclohexane and cycloheptane derivatives **40** and **41**, respectively, in good yields with excellent enantioselectivity (Figure 2). A butynyl-substituted β-keto ester with catalyst **21** gave cyclobutane **42** in lower yield and diminished ee, suggesting that the method may not be suited to the synthesis of strained rings.

Carbocyclization of acyclic substrates leading to products such as **24**−**28** generates a cyclopentane substituted with three flexible functional groups. In an application using all three of these

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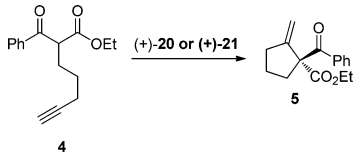
Table 3. Asymmetric Conia-ene Cyclization of β-Keto Ester 4 Catalyzed by Iron−Salen Complexes (+)-20 and (+)-21[a]



					product 5	
entry	catalyst (mol %)	solvent	T [°C]	t [h]	yield [%][b]	ee [%][c]
1	(+)-**20** (5)	DCE	70	18	78	71
2	(+)-**21** (5)	DCE	70	21	72	84
3	(+)-**21** (5)	PhMe	70	24	69	76
4	(+)-**21** (5)	$CHCl_3$	60	24	93	87
5	(+)-**21** (7.5)	$CHCl_3$	60	24	96	90
6	(+)-**21** (7.5)	$CHCl_3$	50	38	93	93

[a]The reactions were carried out on a 0.25 mmol scale in a 0.0625 M solution. [b]Yields of isolated products. [c]Determined by HPLC using a Chiralcel OD column.

functionalities (Scheme 4), diene **28** underwent ring-closing metathesis with Grubbs catalyst[12] to afford indenone **43**, in which the ketone was converted to diester **45** by Wittig olefination with phosphorane **44**. Dieckmann cyclization of **45** gave **46**, and after decarbomethoxylation and conjugate reduction of dienone **47** with Stryker's reagent,[13] fused tricycle **48** was obtained.[14]

With more highly substituted racemic alkynyl ketones **49**−**51**, cyclization of a 1:1 mixture of syn and anti isomers with catalyst **21** resulted in kinetic resolution to give *exo*-methylenecyclopentanes **52**−**54** with high ee (Table 5).[15] Uncyclized substrates **55**−**57** remained as a 1:1 diastereomeric mixture. This result suggests that a substituent β to the ketone in the cyclization substrate can interact sterically with the salen ligand in a manner that leads to diastereoselection and efficient kinetic resolution.

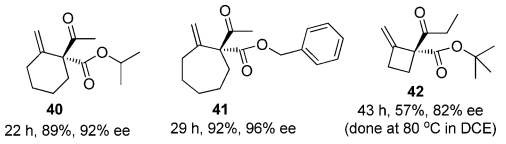
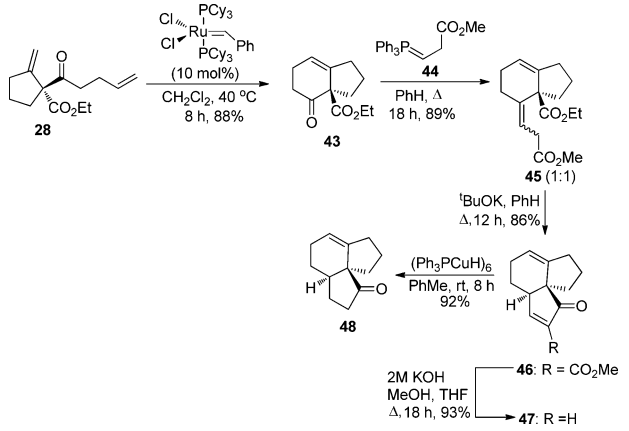


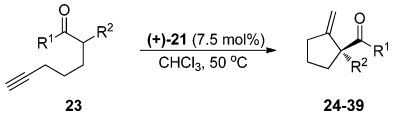
Figure 2. Enantioselective synthesis of four-, six-, and seven-membered carbocycles via Conia-ene cyclization.

Scheme 4. Synthesis of Fused Tricyclic Ketone 48 from Conia-ene Product 28



The formation of *exo*-methylenecyclopentane **5** from keto ester **4** in the presence of salen complex **21** can be explained by complex **58** (Figure 3). In this representation, Fe(III) serves to simultaneously activate the alkyne and promote (*Z*)-enolate formation, thus removing the need for a dual catalyst system.[16] The planar iron enolate is believed to occupy the lower front quadrant below the bicyclic scaffold of the catalyst, as proposed in previous explanations for the stereochemical outcome of reactions involving metal−salen catalysts based on (−)-**3**,[7,8] and

Table 4. Asymmetric Conia-ene Cyclization of α-Functionalized Ketones Catalyzed by (+)-21: Substrate Scope[a]



				product	
entry	R^1	R^2	t [h]	yield [%][b]	ee [%][c]
1	Me	CO_2Me	16	**24**: 96	94
2	Me	CO_2Et	16	**25**: 92	97
3	Me	$CO_2{}^tBu$	24	**26**: 95	97
4	Me	CO_2PMB	18	**27**: 97	97
5	$CH_2{=}CH_2CH_2CH_2$	CO_2Et	23	**28**: 92	96
6	Me	COSPh	28	**29**: 90	92
7	Ph	CO(morpholinyl)	44	**30**: 94	95
8	cyclopropyl	NO_2	18	**31**: 98	96
9	2-furyl	NO_2	24	**32**: 91	92
10	2-thiophenyl	NO_2	20	**33**: 91	97
11	Me	$PO(OMe)_2$	26	**34**: 91	93
12	Me	SO_2Ph	28	**35**: 97	92
13	Me	Ts	19	**36**: 91	98
14	$4\text{-}BrC_6H_4$	CN	39	**37**: 89	94
15	$4\text{-}BrC_6H_4$	SCN	33	**38**: 93	90
16	$4\text{-}BrC_6H_4$	S^nPr	48	**39**: 80	96

[a]The reactions were carried out on a 0.25 mmol scale in a 0.0625 M solution. [b]Yields of isolated products. [c]Determined by HPLC using a Chiralcel OD, AD, OJ, OD-H, or AS-H column.

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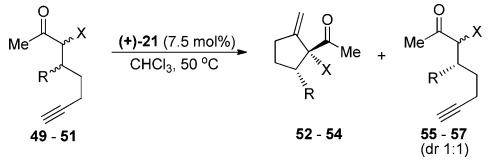
Table 5. Effect of a β-Substituent on Asymmetric Conia-ene Cyclization of α-Functionalized Ketones Catalyzed by (+)-21: Kinetic Resolution[a]



				cyclized product			
entry	R	X	t [h]	conv. [%][b]	yield [%][c]	ee [%][c]	55–57 [%][c]
1	Me	CO_2Me	24	**52**: 48	47	99	**55**: 43
2	Ph	CO_2Me	29	**53**: 46	43	96	**56**: 46
3	Me	SO_2Ph	19	**54**: 47	46	98	**57**: 44

[a]The reactions were carried out on a 0.25 mmol scale in a 0.0625 M solution. [b]Determined by ^1H NMR analysis. [c]Yields of isolated products. [c]Determined by HPLC using a Chiralcel OD-H or AS-H column.

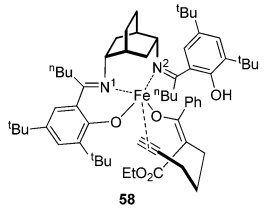


Figure 3. Proposed transition state for the asymmetric Conia-ene synthesis of β-keto ester **4** catalyzed by Fe(III)–salen complex (+)-**21**.

in this orientation the alkyl substituent R attached to the imine carbon of the salen ligand blocks the *si* face of the enolate. The 5-exo-dig cyclization that follows from this configuration leads to *re* face attack by the alkyne and to (*R*)-**5**.

In summary, iron(III)–salen complex **21** derived from a *cis*-2,5-diaminobicyclo[2.2.2]octane scaffold in which the salen ligand carries *n*-butyl substituents on each of the imine carbons has been found to catalyze Conia-ene-type carbocyclization of α-alkynyl-β-keto esters and other α-alkynyl ketones bearing an electron-withdrawing substituent. Complex **21**, the first chiral Fe(III)-based catalyst devised for this purpose, delivers *exo*-methylenecyclopentanes possessing an adjacent stereogenic quaternary center in good yields with high ee. The method is also applicable to asymmetric preparation of four-, six-, and seven-membered rings containing an *exo*-methylene function and geminal ester and keto groups. A reaction mechanism is proposed in which the Fe(III) core of **21** performs the dual role of alkyne activation and enolate partner in a chiral venue where one face of the enolate is blocked to intramolecular attack by the alkyne by a *n*-butyl group of the salen ligand.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) It was recently reported that $FeCl_3$ in DCE at 70–80 °C can catalyze Conia-ene cyclization of **4** in the absence of a cocatalyst. See: Chan, L. Y.; Kim, S.; Park, Y.; Lee, P. H. *J. Org. Chem.* **2012**, *77*, 5239.

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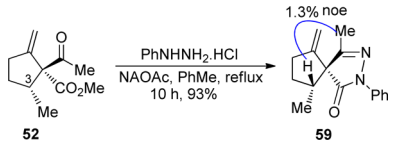
(14) Tricycle **48** can be viewed as a surrogate for the BCD ring system of the mangicols. See: Renner, M. K.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2000**, *65*, 4843.

(15) The relative configuration of **52** was established by reaction with phenylhydrazine hydrochloride to give spiropyrazolinone **59**, in which nuclear Overhauser enhancement was observed between NMR signals due to the proton at C3 of the cyclopentane and the methyl substituent of the heterocycle.



(16) A similar mechanism has been proposed by Hatakeyama for indium-catalyzed Conia-ene-type carbocyclization (see: Hatakeyama, S. *Pure Appl. Chem.* **2009**, *81*, 217). However, alternative mechanisms for metal-catalyzed Conia-ene cyclizations have been considered that do not invoke a metal enolate (see refs 3i, 9, and 10).