JOC Article

Development of a New and Practical Route to Chiral 3,4-Disubstituted Cyclopentanones: Asymmetric Alkylation and Intramolecular Cyclopropanation as Key C−C Bond-Forming Steps

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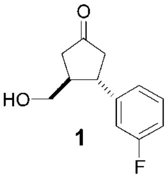
An efficient and practical asymmetric synthesis of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)-cyclopentanone (**1**) is described. An asymmetric Mo-catalyzed alkylation reaction was used to establish the first stereocenter and a Cu-catalyzed intramolecular diastereoselective cyclopropanation reaction was used to set the second stereocenter. The last step involved a one-pot ring-opening/deprotection/hydrolysis/decarboxylation sequence that furnished the desired product in good yield.

Introduction

Substituted cyclopentanones are found in numerous pharmacologically active compounds,[1] and are versatile synthetic intermediates for the preparation of target molecules containing a substituted cyclopentane subunit.[2] In the latter context, cyclopentanone **1** was recently identified as an advanced key intermediate in the synthesis of an investigational new drug candidate at Merck & Co. Accordingly, we required a rapid and efficient asymmetric synthesis of **1** from readily available starting materials in order to furnish necessary quantities of our investigational drug for preclinical and clinical studies.



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The asymmetric synthesis of optically active *trans*-3,4-disubstituted cyclopentanones directly from a readily available cyclopentanone precursor is not straightforward given that the carbons at the 2- and 5-position are significantly more reactive than the carbons at the 3- and 4-positions. For this reason, successful synthetic routes have typically employed either an intermolecular cycloaddition reaction of two functionalized components[3] or an intramolecular cyclization reaction of a properly substituted acyclic precursor. In the latter approach, methods used to effect intramolecular cyclization include classical methods such as a Dieckman cyclization[4] and an aldol reaction,[5] as well as newer methods such as a rhodium-catalyzed cyclization of 3,4-disubstituted 4-pentenals,[6] a rhodium-catalyzed cyclization of carbenoid precursors,[7] a ruthenium-catalyzed three-component coupling followed by a Nozaki−Kishi reaction,[8] and a Pd-catalzyed addition of 1,3-diones to unactivated olefins.[9] Our approach in the synthesis of **1** was based on identifying a properly substituted substrate that can potentially undergo cyclization by various means with minimal chemical steps.

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(1) (a) Elks, J.; Ganellin, C. R. In *Dictionary of Drugs: Chemical Data, Structures and Bibliographies*, 1st ed.; Chapman and Hall: New York, 1990. For reviews see: (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (c) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719. (d) Hudlicky, T.; Rulin, F.; Lovelace, T. C.; Reed, J. W. In *Studies in Natural Products Chemistry*; Atta-ur Rahman, Ed.; Elsevier: Oxford, UK, 1989; Vol. 3, Part B, pp 3−72.

(2) For reviews of cyclopentane synthesis see: (a) Ramaiah, M. *Synthesis* **1984**, 529−570. (b) Hudlicky, T.; Price, J. D. *Chem Rev.* **1989**, *89*, 1467−1486. (c) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. (d) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 455−612. For examples in prostaglandin synthesis see: (e) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; pp 298−322.

(3) For reviews of [3+2] cycloaddition reactions, see: Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, Chapter 3.1, pp 239−270. (b) Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, Chapter 3.2, pp 271−314.

(4) Boeckman, R. K., Jr.; Napier. J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152−4154.

(5) (a) Wenkert, E.; Greenberg, R. S.; Raju, M. S. *J. Org. Chem.* **1985**, *50*, 4681−4685. (b) Pecuniosos, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 2614−2617.

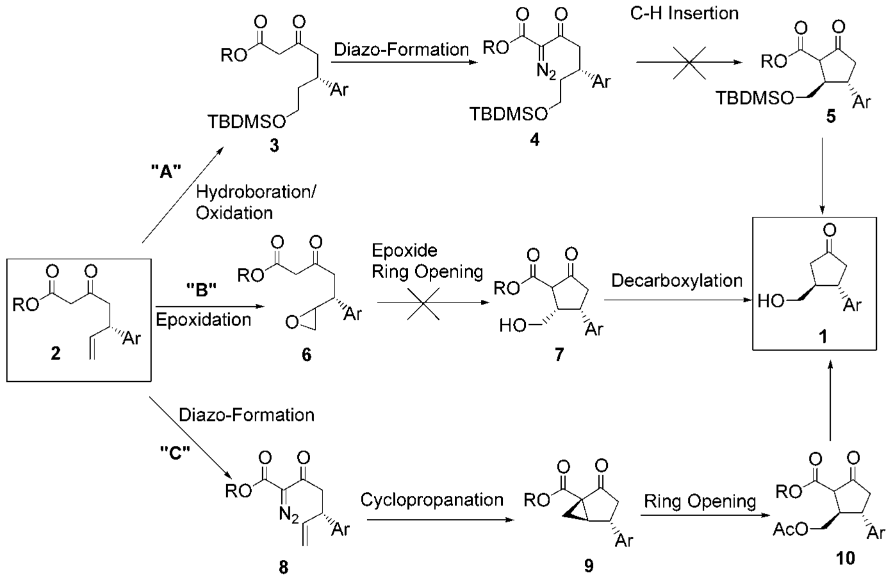
(6) Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 5927−5930.

(7) (a) Taber, D. F.; Ruckle, R. E., Jr. *Tetrahedron Lett.* **1985**, *26*, 3059−3062. (b) Taber, D. F.; Hoerrner, R. S. *J. Org. Chem.* **1992**, *57*, 441−447.

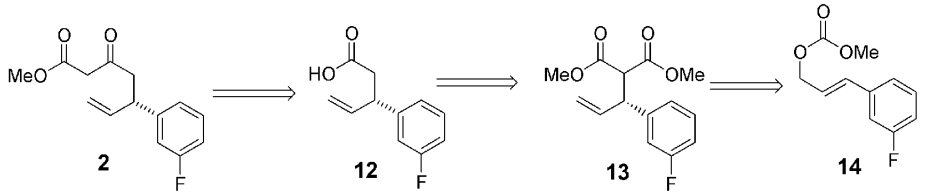
(8) Trost, B. M.; Pinkerton, A. B. *J. Org. Chem.* **2001**, *66*, 7714−7722.

10.1021/jo025890a CCC: $22.00

SCHEME 1

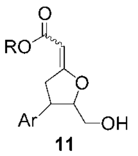


SCHEME 2



Acyclic precursor **2** was identified as an initial target because it contained the desired substituted functionality and because a number of synthetic pathways were envisioned that could be used to synthesize **1** from **2** (Scheme 1). For example, pathway **A**, shown in Scheme 1, utilizes a transition metal-catalyzed C−H insertion as the key cyclization step. Pathway **B** utilizes an intramolecular epoxide ring opening to form the desired five-membered ring, and pathway **C** utilizes an intramolecular cyclopropanation reaction to provide the core cyclopentanone ring system.

Preliminary results from our efforts to use either routes **A** or **B** were disappointing.[10] Our attempt to effect a Rh-catalyzed intramolecular C−H insertion of intermediate **4** to give **5** provided, instead, a complex mixture of byproducts. The intramolecular epoxide ring opening of intermediate **6** afforded the *O*-alkylated ring-opened product **11** as the major product, via alkylation of the ketone oxygen. By comparison, we found that utilization of route **C** eventually provided the desired cyclopentanone product **1**. The route involved the development of several highly selective reactions including a Mo-catalyzed asymmetric alkylation, a Cu-catalyzed intramolecular cyclopropanation, and a one-pot, four-step reaction sequence involving a cyclopropane ring-opening, deprotection, hydrolysis, and decarboxylation. The results and efforts used therein are discussed below.



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Results and Discussion

Our retrosynthetic approach toward the synthesis of **2** is shown in Scheme 2. We envisioned that **2** could be obtained from the chiral acid **12** via chain extension using the protocol of Masamune. Chiral acid **12** can be derived from the malonate derivative **13**. The synthesis of **13** would be the key stereodefining step and would be accomplished via molybdenum-catalyzed asymmetric allylic alkylation of carbonate **14** with dimethyl malonate.

Asymmetric Alkylation Reaction. Recently, significant efforts have been focused on the development of a transition metal-catalyzed asymmetric allylic alkylation of unsymmetrically substituted allylic derivatives for the preparation of optically active branched regioisomers in high enantioselectivity and regioselectivity.[11] In this field, Trost et al. have developed one of the most promising methods involving the use of $(EtCN)_3Mo(CO)_3$/ligand **15** (Scheme 3). The results published by Trost using this system suggested to us that the molybdenum-catalyzed

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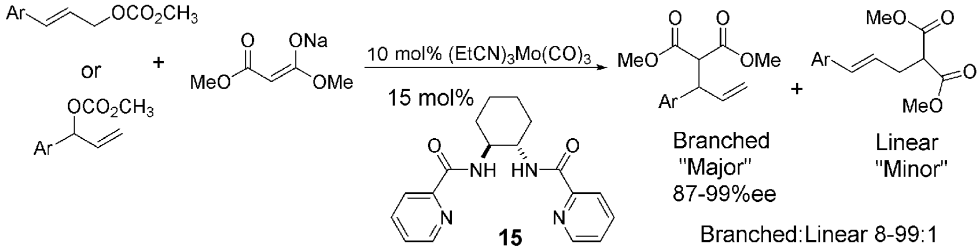
[9] Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290−11291.

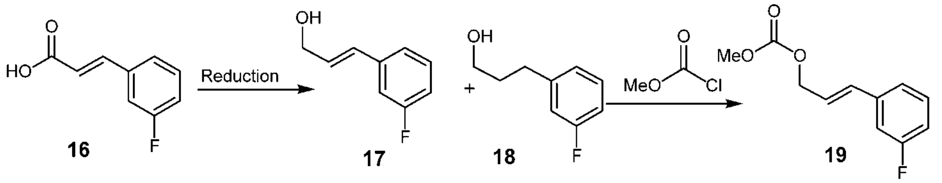
[10] These preliminary results (routes A and B) will be published elsewhere.

[11] (a) Lloyd-Jones, G. C.; Pflatz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462−464. (b) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025−8026. (c) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104−1105. (d) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581−5582. (e) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141−144.

SCHEME 3



SCHEME 4



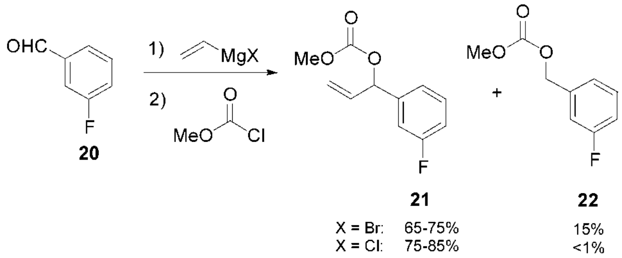
	17	18
$NaBH_4/I_2$	80	20
$LiAlH_4$	93	7

asymmetric alkylation methodology would be well-suited for the preparation of the desired product **13** in good enantio- and regioselectivity from an allyl carbonate precursor.

The use of linear allyl carbonates in the molybdenum-catalyzed asymmetric alkylation reaction has been shown to produce slightly better enantioselectivity and regioselectivity than branched racemic carbonates.[11c,e] Consequently, our initial efforts focused on the synthesis of the linear carbonate. Starting with 3-fluorocinnamic acid **16**, we sought to carry out a two-step procedure involving the reduction of the acid to the alcohol **17**, followed by carbonate formation via reaction with methyl chloroformate to provide **19**, Scheme 4. However, our attempts to reduce the acid to the alcohol were accompanied by reduction of the double bond to produce **18**. With use of either $NaBH_4/I_2$ or $LiAlH_4$, a substantial amount of the over-reduced product was observed along with multiple unidentified byproducts as determined by HPLC.[12] These results coupled with the fact that the branched allyl carbonate **21** can be made in one pot, vide infra, led us to abandon the use of the linear carbonate as a possible starting allyl carbonate.

For the synthesis of the racemic branched allyl carbonate **21**, we focused on the development of a one-pot method consisting of vinyl Grignard addition to aldehyde **20**, followed by trapping of the magnesium alkoxide intermediate with methyl chloroformate, Scheme 5. With use of vinylmagnesium bromide, benzylic carbonate **21** was formed in up to 15%, suggesting that reduction of aldehyde **20** was competitive. Transmetalation of the vinylmagnesium bromide from magnesium to zinc via addition of $ZnCl_2$ suppressed the reduction pathway to 10%. However, it was found that using vinylmagnesium chloride in place of the bromide reduced the formation of impurity **22** to <1%, and that transmetalation to zinc was unnecessary. By using toluene as solvent for ease of workup, carbonate **21** was formed in 76−85% yield in one pot from aldehyde **20**.

SCHEME 5



Results from preliminary studies on the asymmetric alkylation of carbonate **21** with sodiodimethyl malonate using the Trost catalyst system were promising: 75−90% yield, 88−96% ee, regioselectivity of 6−20:1 branched:linear. However, it became evident that direct implementation of the reaction protocol to large-scale production would not be straightforward due to the limited availability of the precatalyst $(EtCN)_3Mo(CO)_3$ and ligand **15**, both of which were not commercially available during this study.[13] Consequently, our efforts turned to developing a simple procedure for the preparation of ligand **15**, and the use of a more readily available Mo precatalyst. These studies, which have been communicated recently, culminated in an improved and practical synthesis of ligand **15**, as well as the use of the readily available, cost-effective, and air-stable $Mo(CO)_6$ as the molybdenum precatalyst.[14] These improvements allowed us to perform the reaction on multikilo scale numerous times, while affording the desired branched product in 84−91% yield and in 96−97% ee (Scheme 6).[15]

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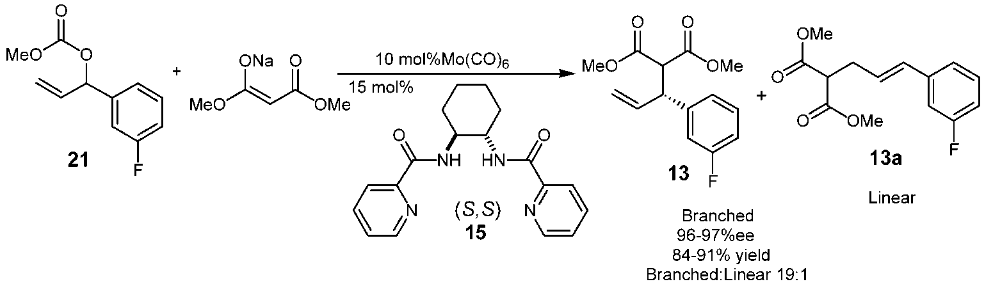
(12) (a) Bhaskar Kanth, J. V.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964−5965. (b) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 2548−2549.

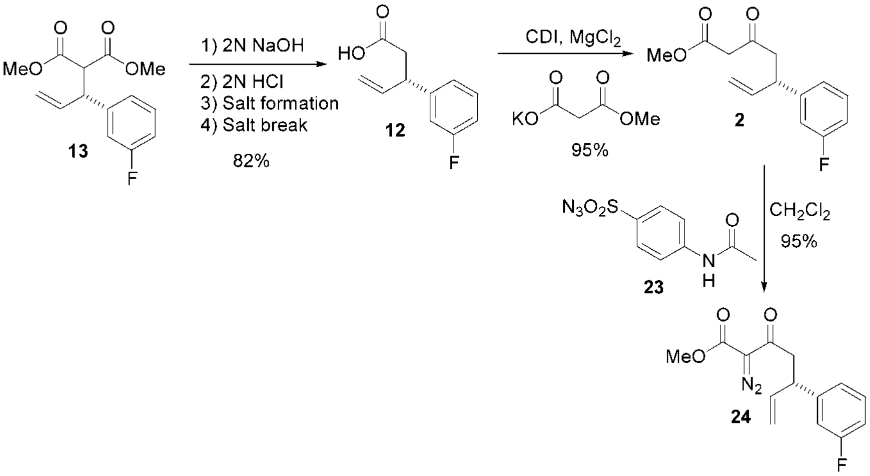
(13) Strem Chemical Company currently sells ligand **15**.

(14) (a) The development of the Mo-catalyzed asymmetric reaction employing $Mo(CO)_6$ as precatalyst to prepare compound **13** including optimization and other experimental results are described in the following communication: Palucki, M.; Um, J. M.; Conlon, D. A.; Yasuda, N.; Hughes, D. L.; Mao, B.; Wang, J.; Reider, P. J. *Adv. Synth. Catal.* **2001**, *343*, 46−50. (b) Conlon, D. A.; Yasuda, N. *Adv. Synth. Catal.* **2001**, *343*, 137−138.

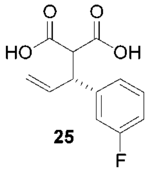
SCHEME 6



SCHEME 7



Preparation of the α-Diazo-*β*-ketoester Intermediate 24. Solvolysis/decarboxylation of **13** to provide monoacid **12** was first accomplished by heating a dioxane solution of **13** at reflux in the presence of 6 N HCl (aq), Scheme 7. However, the yields obtained with these conditions varied to a large degree (48−80%), due to a competitive acid-catalyzed lactonization pathway that afforded lactone **28**. Intermediates that were observed during the course of the reaction include the diacid **25**, monoacid-monoester **26**, and the monoester **27**.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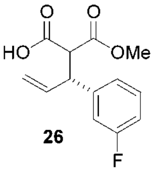
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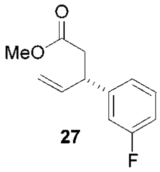
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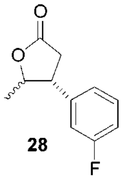
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Because of the problems encountered in the one-pot hydrolysis/decarboxylation of **13**, efforts to develop a stepwise protocol were initiated. Acid hydrolysis was first studied; however, the results were discouraging. High concentrations of aq HCl in the presence of an organic cosolvent (THF, 1,4-dioxane, and DMF) resulted in fast starting material conversion, but provided lactone **28** as the major product. Low concentrations of acid minimized formation of **28**, but starting material conversion was very slow. In contrast, base hydrolysis with dilute NaOH and no cosolvent was found to be fast and effective in producing diacid **25**. The subsequent decarboxylation was carried out in the same reaction vessel by adjusting the pH to 1 using concentrated HCl and heating for 12 h to provide **12** in good yield. The major byproduct of the reaction was methyl ester **27**, which increased proportionally at lower pH values. Formation of **27** was suppressed by the removal of MeOH after the base hydrolysis portion of the sequence. Isolation and purification of **12** was accomplished via salt formation with the amine base (*S*)-*sec*-phenethylamine.[16] The stereochemical integrity of the stereogenic benzylic carbon was maintained throughout these studies.

Chain extension of **12** using the protocol of Masamune provided the *β*-ketoester **2** in excellent yield.[17] Formation of the diazo-compound **24** was accomplished in excellent yield via reaction of *β*-ketoester **2** with 4-acetomidobenzenesulfonyl azide.[18] Because of the general thermal instability of α-diazo compounds the product was not isolated, but rather used directly as a solution in the subsequent diastereoselective intramolecular cyclopropanation reaction.

Diastereoselective Intramolecular Cyclopropanation Reaction. Stereoselective cyclopropanation reac-

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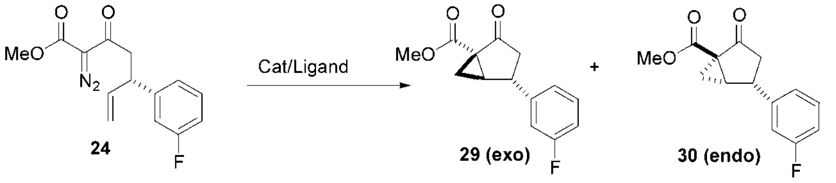
(15) The workup of the asymmetric alkylation reaction was comprised of a single water wash followed by filtering the toluene solution through a small silica gel pad to remove any molybdenum residues as well as ligand **15**. The resulting filtrate was concentrated and used directly in the subsequent reaction. Crystallization of **13** from toluene was accomplished with an upgrade in ee (>99% ee and >99% chemical purity); however, a 20% loss of **13** in the filtrate was incurred.

(16) On laboratory scale (1 g), an upgrade in ee of **12** was observed with salt formation/salt break of **17** with (*S*)-*sec*-phenethylamine; however, on large scale (1 kg), no increase in ee was observed.

(17) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72−74.

(18) Davies, H. M. L.; Cantrell, W. R.; Romines, D. R.; Baum, J. S. *Org. Synth.* **1993**, *70*, 93−100.

SCHEME 8



tions of α-diazocarbonyls are catalyzed by a large number of transition metal complexes, of which Cu and Rh complexes have emerged as the most prominent catalysts.[19,20] In our synthesis, we required a diastereoselective intramolecular cyclopropanation of **24** to provide the desired exo cyclopropane product **29** in preference to the endo cyclopropane product **30**, Scheme 8. Although we were unable to find literature precedent for achieving the desired diastereoselectivity, we felt that through some catalyst screening, we could identify a catalyst that would effect the reaction with the required selectivity.[21] At the minimum, we hoped that the use of a chiral catalyst would potentially provide match/mismatch interactions between itself and the chiral substrate to effect the desired reaction in high diastereoselectivity.

Our first attempt at screening transition metal catalysts involved the use of achiral rhodium dimer complexes. Intramolecular cyclopropanation reactions of **24** catalyzed by rhodium dimer complexes were typically characterized by complete starting material conversion with minimal byproduct formation. Although these reactions were clean and fast, the undesired endo isomer **30** was obtained as the major product (Table 1, entries 1−3).

The use of achiral copper catalysts in the intramolecular cyclopropanation reaction provided better selectivities overall compared to rhodium dimer complexes (Table 1, entries 4−11). In contrast to reactions catalyzed by the rhodium dimer complexes, cyclopropanation reactions with copper catalyst were very sluggish at room temperature and required heating to 75 °C in 1,2-dichloroethane to achieve reasonable rates. A comparison of various copper sources shows that copper catalysts containing moderately coordinating ligands (Table 1, entries 4−8) exhibited lower diastereoselectivty than copper catalysts containing weakly or noncoordinating ligands (Table 1, entries 9 and 10). Indeed, the most selective catalyst was generated from reaction of CuCl with AgOTf to produce CuOTf.

Because **24** is chiral, the potential for identifying match/mismatch interactions with chiral catalysts is possible. Both chiral rhodium and copper catalysts were examined and the results of these studies are shown in Table 2.

TABLE 1. Intramolecular Cyclopropanation Reaction of 24 with Achiral Rh and Cu Catalysts[a]

entry	catalyst	solvent	temp (°C)	conversion (%)[c]	**29**:**30**[d]
1	$Rh_2(OAc)_4$	CD_2Cl_2	rt	100 (90)	43:57
2	$Rh_2(Octa)_4$	CD_2Cl_2	rt	100 (87)	33:67
3	$Rh_2(CAP)_4$	CD_2Cl_2	rt	95	33:67
4	CuCl	1,2-DCE	75	99	50:50
5	$Cu(acac)_2$	1,2-DCE	75	37	54:46
6	CuOAc	1,2-DCE	75	88	46:54
7	Cu_2O	1,2-DCE	75	3	42:58
8	CuSCN	1,2-DCE	75	10	70:30
9	$Cu(OTf)_2$	1,2-DCE	75	100 (92)	77:23
10	$[(CH_3CN)_4Cu]PF_6$	1,2-DCE	75	100 (98)	83:17
11[b]	CuCl/AgOTf	1,2-DCE	75	100 (89)	85:15

[a] Entries 1−3, 10, and 11 were performed with 1 mol % of catalyst and at 0.1 M **24**. Entries 4−9 were performed with 5−15 mol % of catalyst and at 0.2 M **24**. [b] A ratio of 1:1.2 was used for CuCl/AgOTf. [c] The numbers in parentheses are isolated yields of combined **29**/**30**. [d] The ratio of **29**/**30** was determined by HPLC by using a Zorbax SB-−C18 column 4.6 × 250 mm.

As shown in Table 2, the use of chiral catalysts did not improve the diastereoselectivitiy for the intramolecular cyclopropanation of **24**. Four commercially available chiral Rh catalysts were examined with the idea of improving the diastereoselectivity through match/mismatch interactions with the chiral substrate.[22] Unfortunately, all of the Rh catalysts displayed only modest diastereoselectivity. In contrast to the achiral Rh catalyst, reactions with these catalysts were extremely slow at room temperature and required heating to 60 °C to achieve reasonable rates of reaction. Similarly, the use of chiral copper complexes of bis-oxazolines provided only modest diastereoselectivity.[23] These results coupled with the results shown in Table 2 with achiral copper complexes suggest that a ligand free copper catalysts is best for preferentially forming the desired product **29** over **30**.

Transition metals other than copper or rhodium were also examined, including $Ni(acac)_2$, $NiCl_2$, $CoCl_2$, $Co(acac)_3$, $Yb(OTf)_3$, and $[RuCl_2(p\text{-cymene})]_2$; however, except for $[RuCl_2(p\text{-cymene})]_2$, the starting material conversion with these catalysts was less than 5%. The use of $[RuCl_2(p\text{-cymene})]_2$ gave complete conversion of the starting material, but with a **29**:**30** ratio of 35:65.

The catalysts that provide the highest desired diastereoselectivity for the intramolecular cyclopropanation of **24** are $[(CH_3CN)_4Cu]PF_6$ and CuCl/AgOTf. In both cases, the reactions can be carried out at low catalyst loading. In the presence of strongly coordinating ligands, the diastereselectivity is lower and the rate of reaction is slower.

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(19) For a review on asymmetric cyclopropanations with Rh catalysts, see: (a) Lydon, K. M.; McKervey, M. A. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Chapter 16.2, pp 539−580. For a review on asymmetric cyclopropanations with Cu catalysts see: (b) Pfaltz, A. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Chapter 16.1, pp 513−538. For a review on asymmetric catalytic metal carbene transformation, see: (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935.

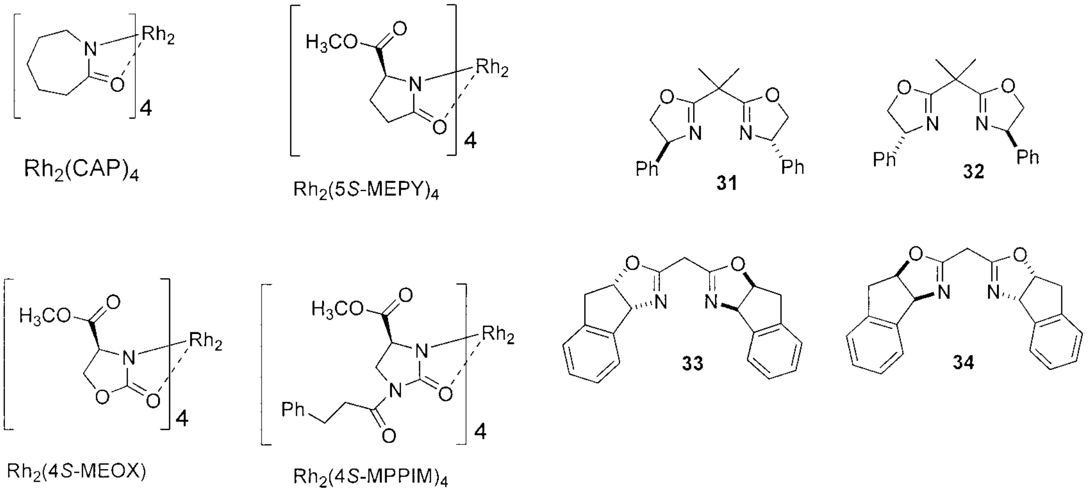
(20) For reviews on asymmetric synthesis with diazo compounds, see: (a) Calter, M. A. *Current Org. Chem.* **1997**, *1*, 37−70. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. (c) Adams, J.; Spero, D. *Tetrahedron* **1991**, *47*, 1765−1808.

(21) For examples of diastereoselective intramolecular cyclopropanation reactions, see: (a) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 11022−11022. (b) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493−4494.

(22) Doyle, M. P. *Aldrichim. Acta* **1996**, *29*, 3−11.

(23) For a review on bis-oxazolines in asymmetric synthesis see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Asymmetry.* **1998**, *9*, 1−45.

TABLE 2. Cyclopropanation of 24 with Chiral Catalysts[a]



entry	catalyst	ligand	conversion (%)	**29**:**30**[b]
1	$Rh_2(5S\text{-MEPY})_4$		71	42:58
2	$Rh_2(5R\text{-MEPY})_4$		90	52:48
3	$Rh_2(4S\text{-MEOX})_4$		77	48:52
4	$Rh_2(4S\text{-MPPIM})_4$		44	30:70
5	$[(CH_3CN)_4Cu]PF_6$	**31**	100	60:40
6	$[(CH_3CN)_4Cu]PF_6$	**32**	100	54:46
7	$[(CH_3CN)_4Cu]PF_6$	**33**	100	59:41
8	$[(CH_3CN)_4Cu]PF_6$	**34**	100	52:48

[a] For entries 1−4, reactions were performed with 5 mol % of catalyst at 0.1 M **24** in 1,2-dichloroethane. For entries 5−8, reactions were performed with 20 mol of Cu and 22 mol % of ligand at 0.1 M **24** in 1,2-dichloroethane. [b] The ratio of **29**/**30** was determined by HPLC by using a Zorbax SB-C18 column 4.6 × 250 mm.

In addition, based on the trans orientation of the substituents on the cyclopentane ring product, one could predict that **29** would be the major diastereomeric product. However, Molecular Mechanics calculation show a ground-state energy difference between **29** and **30** to be only 1.3 kcal.[24] Additionally, cyclopropanation reactions are thought to occur through an early transition state, thus minimizing the influence of product ground-state energy differences on diastereoselectivity. Further studies are clearly needed to determine if the resulting diastereoselectivity with and without added ligands is due to nonbonding interaction in the transition state or to different mechanistic pathways.[25]

Because of the general thermal instability of diazo compounds, a solution of **24** in 1,2-dichloroethane was slowly added over 4 h to a catalyst solution at 75 °C. By using this protocol, a minimal buildup of **24** occurs during the course of the reaction. Upon reaction completion, the mixture was concentrated, filtered through a small pad of silica gel, and used directly in the next reaction.

Ring Opening/Deprotection/Hydrolysis/Decarboxylation. Our initial approach for forming **1** from a mixture of **29**/**30** was to develop a two-step process. The first step would involve ring opening the cyclopropane ring with sodium or potassium acetate in a polar aprotic solvent such as DMF or DMSO to yield **35** (Scheme 9).[26] The second step would involve removal of the acetate and hydrolysis/decarboxylation of the methyl ester to furnish **1**. In our very first attempt at ring opening **29**/**30** (5 equiv of NaOAc in DMF at 100 °C), we were pleased to find that **1** was formed in 30% yield. Most interesting was that the cis product derived from ring opening of **30** was not observed. Although this result affirms that we can directly obtain **1** from **29**/**30** in a one-pot procedure, we quickly found that product yields were not always reproducible.

Further studies in the optimization of this reaction led to two key advancements in the reaction protocol. The first was the addition of 5 equiv. of AcOH, which consistently effected complete conversion of the starting cyclopropane. The second involved changing the workup of the reaction. Although efforts to use anhydrous solvents and reagents were undertaken, clearly the presence of adventitious water facilitated the deprotection/hy-

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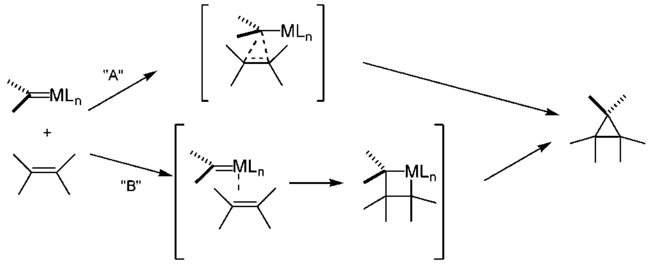
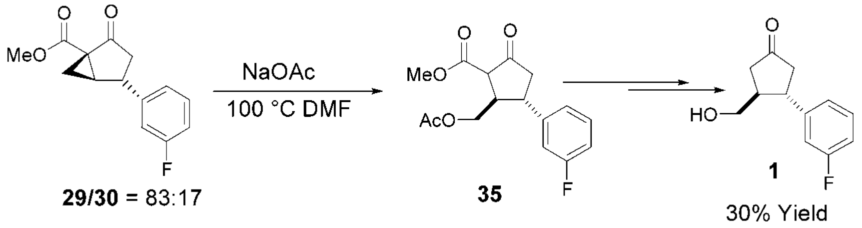
(24) Molecular Mechanics calculations performed on PC SPARTAN PRO 6.0.6.

(25) Two different mechanisms have been proposed for the formation of the cyclopropane ring: (1) Mechanism A, which proceeds via a concerted pathway, and (2) Mechanism B, which proceeds via a two-step pathway involving a metallocyclobutane followed by reductive elimination to the cyclopropane product. Mechansim B may be favored by catalyst systems devoid of ligands, whereas mechanism A may be relatively favored by the sterically demanding chiral ligands.

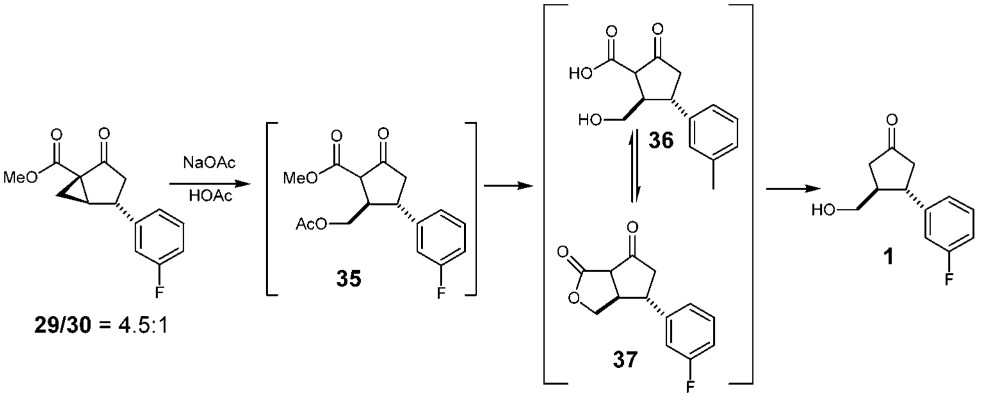


(26) (a) Tanimori, S.; Tsubota, M.; He, M.; Nakayama, M. *Synth. Commun.* **1997**, *27*, 2371−2378. (b) Tanimori, S.; Tsubota, M.; He, M.; Nakayama, M. *Biosci. Biotechnol. Biochem.* **1995**, *61*, 2091−2093.

SCHEME 9



SCHEME 10



drolysis/decarboxylation sequence. Consequently, a two-step, one-pot protocol was developed in which a solution of **29**/**30**, HOAc, and NaOAc in DMF was heated at 100 °C for 12−15 h followed sequentially by cooling to room temperature, adding 5 N NaOH until pH >11, and heating at 60 °C for 30 min to ensure complete decarboxylation. With use of this procedure, the desired cyclopentanone **1** was reproducibly obtained in 50−60% yield.

Although the two-step, one-pot protocol provided the desired ring-opened product in moderate yield, a significant percentage of the starting material was still unaccounted for. ^{1}H NMR of the crude reaction mixture revealed that a byproduct identified as deriving from ring opening of the cyclopropane ring with dimethylamine was formed in about 15−25%. This is not surprising as DMF is known to decompose to dimethylamine and carbon monoxide at high temperatures and that dimethylamine is substantially more nucleophilic than sodium acetate.

To avoid the formation of the dimethylamine byproduct, other polar, aprotic solvents were investigated including DMAc, DMSO, and NMP. Reactions in these solvents were found to be much slower and provided multiple byproducts as determined by HPLC. Further solvent studies led to the use of HOAc directly as solvent. Reactions with HOAc were fast; however, the reaction was accompanied by approximately 6% of the cis ring-opened product. This byproduct posed minimal problems as it was easily removed in subsequent reactions. Using the new procedure, a one-pot ring-opening/deprotection/hydrolysis/decarboxylation reaction sequence provided the desired product **1** in 86−94% yield from **29**.

The remarkable transformation of a mixture of cyclopropanes **29** and **30** to cyclopentanone **1** involves multiple bond-making and bond-breaking steps, as well as a selective kinetic resolution of the diastereomeric cyclopropanes. The first step of the sequence involves the ring opening of the cyclopropane ring with acetate to provide intermediate **35** (Scheme 10). A HPLC-MS analysis of a reaction mixture sample prior to the addition of DMF and NaOH (aq) gave a mass of *m*/*z* 308 for the major peak in the chromatogram. The next two steps involve removal of the acetate group and hydrolysis of the methyl ester to give either **36** or lactone **37**. We have synthesized **37** via a different route and have observed that **37** can be converted to **1** under the workup conditions.[27] In addition, HPLC analysis of the reaction mixture shows that a peak appears at the retention time where authentic **37** elutes and subsequently disappears. The final step of the sequence is the decarboxylation of **36** to provide **1**.

Starting with a 82:18 mixture of **29**/**30**, a mixture of the trans cyclopentanone product **1** and its epimer is obtained in a 94:6 ratio. We propose that ring opening of the endo cyclopropane starting material **30** is slow relative to ring opening of the trans cyclopropane starting material **29** due to steric interaction between the aryl group on the cyclopentane ring system and the attacking nucleophile (Scheme 11). The unreacted cyclopropane **30** is hydrolyzed to acid **38** upon addition of DMF and NaOH (aq). Fortunately, the decarboxylation of **38** to **40** does not occur due to its inability to generate the immediate enol product at the bridgehead carbon, and removal of acid **38** is accomplished by a simple base extraction. Overall, this simple protocol effects a one-pot ring-opening/deprotection/hydrolysis/decarboxylation reaction sequence, as well as providing a means of selectively removing the undesired isomer **30**.

Conclusion

In summary, an efficient and practical asymmetric synthesis of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)cyclopentanone (**1**) was accomplished. An asymmetric

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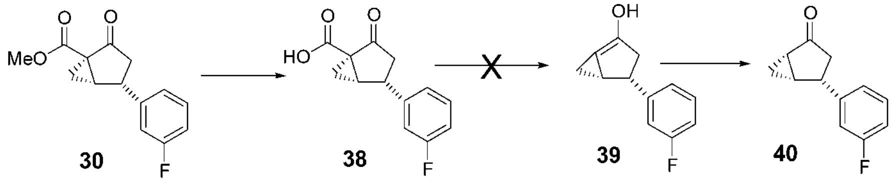
[27] The synthesis of **37** will be reported in due course.

SCHEME 11



Mo-catalyzed alkylation reaction was used to set the first stereocenter. Optimization of this reaction led to significant improvements, including the use of the readily available, air-stable $Mo(CO)_6$ as the molybdenum precatalyst. A diastereoselective Cu-catalyzed intramolecular cyclopropanation reaction led to the establishment of the second chiral center in a 85:15 ratio. Extensive catalyst screening, including chiral catalysts, identified $(CH_3CN)_4CuPF_6$ and CuCl/AgOTf as the most selective catalyst. Finally, a one-pot ring-opening/deprotection/hydrolysis/decarboxylation sequence was used to generate **1** in good yield.

Experimental Section

General Methods. All reactions were performed under an atmosphere of nitrogen unless otherwise specified. NMR spectra were obtained in $CDCl_3$ at 400 MHz for ^1H and 100 MHz for ^{13}C. Elemental analyses were performed by Quantitative Technologies Inc. (Whitehouse, NJ). Silica gel chromatography was performed with 200−400 mesh SiO_2 (EM Science). All commercial reagents and solvents were used as received unless otherwise noted.

(3*S*,4*S*)-3-(3-Fluorophenyl)-4-(hydroxymethyl)cyclopentanone (1). A 72-L round-bottom flask equipped with a temperature probe, overhead stirrer, and nitrogen and vacuum inlet was charged with the **29**/**30** (5:1 exo/endo, 1.60 kg trans, 6.45 mol trans), NaOAc (5.29 kg, 64.5 mol), and HOAc (32 L, 560 mol). The mixture was evacuated and back filled with N_2 (3 cycles) and heated to 105 °C for 15 h. Acetic acid (22 L) was distilled off with slight vacuum while maintaining the temperature above 90 °C. The mixture was then cooled to 80 °C followed by the addition of DMF (27 L) and then cooled to room temperature. To this was added 3 N NaOH (17 L) and then 5 N NaOH (32 L) until pH 12 while maintaining the temperature below 50 °C. The resulting solution was heated to 70 °C for 30 min and then cooled to room temperature. To the mixture was added MTBE (60 L) and the aqueous layer was separated and extracted with MTBE (60 L). The organic layers were combined, washed with 30 L of 10% NaCl in water, dried over $MgSO_4$, filtered, and concentrated to give an assay yield of 1.46 kg of **1** in a 16:1 ratio of trans to cis (90% yield total). Silica gel chromatography on a small sample yielded pure **1** as a clear oil. R_f 0.30 (hex:EtOAc = 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 1H), 7.06 (d, $J = 7.7$ Hz, 1H), 6.98 (m, 2H), 3.73 (dd, $J = 10.7$, 3.8 Hz, 1H), 3.61 (dd, $J = 10.7$, 5.3 Hz, 1H), 3.28 (ddd, $J = 19.0$, 10.7, 8.2 Hz, 1H), 2.75 (dd, $J = 18.5$, 7.9 Hz, 1H), 2.61 (dd, $J = 17.7$, 7.1 Hz, 1H), 2.31−2.51 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 216.1, 163.1 (d, $J_{CF} = 251$ Hz), 144.5 (d, $J_{CF} = 7.2$ Hz), 130.4 (d, $J_{CF} = 8.0$ Hz), 123.0 (d, $J_{CF} = 2.4$ Hz), 114.2 (d, $J_{CF} = 20.9$ Hz), 113.9 (d, $J_{CF} = 20.9$ Hz), 62.5, 47.1, 46.3, 43.9, 41.7. IR (neat, cm^{-1}): 3445, 2914, 1737, 1588. GCMS: m/z 208. The ee was determined to be 98%. HPLC ee analysis (ChiralPak AD-RH, 4.6 × 250 mm, flow rate = 0.5 mL/min, detection at 210 nm, 0.1% H_3PO_4 in H_2O:acetonitrile 60:40): $t_R = 9.5$ min (minor), $t_R = 10.3$ min (major).

Methyl (5*S*)-5-(3-Fluorophenyl)-3-oxo-6-heptenoate (2). A 50-L, 4-necked round-bottom flask, equipped with mechanical stirrer, thermocouple, reflux condenser with N_2 inlet, addition funnel, and steam pot, was charged sequentially with 1,2-dichloroethane (7.2 L), monomethylmalonate potassium salt (1.99 kg, 12.17 mol), and magnesium chloride (830 g, 8.72 mol). The mixture was cooled to 0−5 °C followed by the slow addition of triethylamine (3.55 L, 25.5 mol) over 2−5 min. After being stirred for 30 min at 0−5 °C, the solution was warmed to 20−25 °C and subsequently stirred for 30 min. A 22-L, round-bottom flask, equipped with mechanical stirrer, thermocouple, N_2 inlet, and addition funnel, was charged with 1,2-dichloroethane (5.3 L) and 1,1-carbonyldiimidazole (1.52 kg, 9.37 mol). A 1,2-dichloroethane (2 L) solution of **12** (1.65 kg, 8.50 mol) was added to the CDI slurry over 20 min. After being stirred for 20 min, the CDI/**12** solution was added to the monomethylmalonate solution over 5 min. The resulting solution was heated at 45 °C for 1.5 h and then cooled to 0−5 °C. To the cold mixture was added cold 2 N HCl (25 L). The aqueous phase was separated and extracted with 1,2-dichloroethane (6 L). The 1,2-dichloroethane extracts were combined, dried over anhydrous Na_2SO_4, and filtered and the cake was washed with 1,2-dichloroethane (1 L). The filtrate and washes were combined and concentrated to yield 2.10 kg of **2** (98% yield). Silica gel chromatography on a small sample yielded pure **2** as a colorless oil. R_f 0.44 (hex:EtOAc = 3:1). Colorless oil, 9:1 β-ketoester:enol. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.00 (d, $J = 7.7$ Hz, 1H), 6.92 (m, 2H), 5.94 (ddd, $J = 17.1$, 10.3, 6.8 Hz, 1H), 3.96 (m, 1H), 3.72 (s, 3H), 3.40 (s, 2H), 2.99 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.3, 167.2, 162.9 (d, $J_{CF} = 246.1$ Hz), 145.1 (d, $J_{CF} = 7.2$ Hz), 139.6, 130.0 (d, $J_{CF} = 8.8$ Hz), 123.3 (d, $J_{CF} = 2.4$ Hz), 115.4, 114.5 (d, $J_{CF} = 20.1$ Hz), 113.6 (d, $J_{CF} = 20.1$ Hz), 52.3, 49.5, 47.9, 43.7. IR (neat, cm^{-1}) 2955, 1746, 1717, 1589, 1438. Anal. Calcd for $C_{14}H_{15}FO_3$: C, 67.19; H, 6.04. Found: C, 67.14; H, 6.06.

(3*S*)-3-Phenyl-4-pentenoic Acid (12). A toluene solution of malonic ester intermediate **13** (5.50 kg, 20.66 mol) was charged to a 50-L flask equipped with mechanical stirrer, thermocouple, and condenser. Water (18.3 L) and 5 N NaOH (12.2 L) were added to the flask and the resulting mixture was heated to 90 °C for 1 h. The flask was fitted with a distillation head and a downward condenser, and the mixture was distilled to remove MeOH. The distillation was continued until the level of MeOH byproduct was <3−4 mol % (determined by ^1H NMR). After the distillation was stopped, the mixture was transferred to a 100-L reactor and the pH was adjusted to 1.0 with concentrated HCl (4.63 L). The mixture was refluxed for 15 h then cooled to 20−25 °C, and the organic layer was separated. The aqueous layer was extracted with 18 L of toluene. The first organic layer and the toluene extract were combined and washed with 7.3 L of 5% NaCl (aq). The solution was dried with Na_2SO_4 (2.44 kg), filtered, weighed (19.0 kg, HPLC assay: 3.52 kg product, 90% yield), and used directly in the next reaction. Silica gel chromatography on a small sample yielded pure **12** as an oil. R_f 0.31 (hex:EtOAc = 3:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 1H), 7.01 (d, $J = 7.8$ Hz, 1H), 6.94 (m, 2H), 5.97 (ddd, $J = 17.2$, 10.3, 6.8 Hz, 1H), 5.12 (m, 2H), 3.88 (m, 2H), 2.78 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.0, 163.0 (d, $J_{CF} = 245.7$ Hz), 144.7 (d, $J_{CF} = 7.2$ Hz), 139.2, 130.1 (d, $J_{CF} = 8.0$ Hz), 123.2 (d, $J_{CF} = 3.2$ Hz), 115.6, 114.5 (d, $J_{CF} = 21.7$ Hz), 113.7 (d, $J_{CF} = 21.7$ Hz), 44.8, 39.7. IR (neat, cm^{-1}) 1713, 1614, 1590, 1488. Anal. Calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found: C, 67.52; H, 5.69. The ee was determined to be 98%. HPLC ee analysis (ChiralPak AD-RH, 4.6 × 250 mm, flow rate = 0.5 mL/min, detection at 210 nm, 0.1% H_3PO_4 in H_2O:acetonitrile 68:32): $t_R = 15.0$ min (minor), $t_R = 16.3$ min (major).

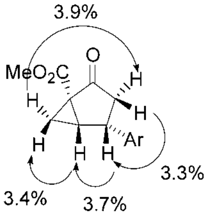
Dimethyl 2-[(1*R*)-1-(3-fluorophenyl)-2-propenyl]pro-

panedioate (13).[28] A 12-L, three-necked round-bottomed flask was charged with $Mo(CO)_6$ (219 g, 0.828 mol) and ligand **15** (402 g, 1.24 mol) and evacuated/back filled with argon (3 cycles). To this was added anhydrous toluene (4.36 L). The flask was evacuated/back filled with argon (3 cycles), and the resulting mixture was heated to 85−88 °C for 4 h. Separately, a 100-L flask was charged with dimethyl sodiomalonate (2.36 kg, 12.42 mol), a toluene solution of carbonate **21** (2.0 kg, 8.28 mol, 3 L of anhydrous toluene), and toluene (30.6 L). The flask was evacuated/back filled with argon and the resulting solution was heated to 70 °C followed by the addition of the catalyst solution via cannula. The resulting mixture was heated to 85 °C for 15 h and subsequently cooled to room temperature. Water (36 L) was added and the organic layer was separated and filtered through a small pad of silica gel. Product assay yield was 91%, with a 97% ee and a 95:5 regioselectivity (branched:linear ratio). The solution was concentrated in vacuo and used directly in the next reaction. Crystallization of a small sample resulted in large crystalline prisms. Mp 34−35 °C. R_f 0.35 (hex:EtOAc = 9:1). 97% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.52 (m, 2H), 7.01 (d, J = 7.7 Hz, 1H), 6.90−6.95 (m, 2H), 5.96 (ddd, J = 17.0, 10.2, 8.2 Hz, 1H), 5.11−5.16 (m, 2H), 4.09−4.14 (m, 1H), 3.84 (d, J = 10.9 Hz, 1H), 3.75 (s, 3H), 3.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J_{CF} = 241 Hz), 154.9, 140.8, 135.2, 130.2 (d, J_{CF} = 10.1 Hz), 122.6, 118.0, 115.3 (d, J_{CF} = 20.1 Hz), 113.9 (d, J_{CF} = 20.1 Hz), 79.3, 54.9. IR (neat, cm^{-1}) 2955, 1732, 1614, 1590, 1489. Anal. Calcd for $C_{14}H_{15}O_4F$: C, 63.15; H, 5.68. Found: C, 62.94; H, 5.63. The ee was determined to be 98%. HPLC ee analysis (ChiralPak AD, 4.6 × 250 mm, flow rate = 0.8 mL/min, detection at 210 nm, 2% MeOH in Hexane): t_R = 9.1 min (minor), t_R = 10.4 min (major).

1-(3-Fluorophenyl)-2-propenyl Methyl Carbonate (21). A 100-L flask equipped with mechanic stirrer, thermocouple, N_2 inlet, and addition funnel was charged with toluene (60 L) and 3-fluorobenzaldehyde (4 kg, 97%, 31.2 mol). After the solution was cooled to −5 °C, vinylmagnesium chloride (20.6 L, 1.6 M in THF, 32.8 mol) was added dropwise over a period of 1.5 h while maintaining the temperature below 0 °C. The reaction was stirred for an additional 60 min at −5 to 0 °C, followed by the addition of methyl chloroformate (2.74 L, d = 1.223, 35.4 mol) over 30 min while maintaining the temperature below 0 °C. After the mixture was stirred for 60 min, 0.5 N HCl (40 L) was added, while maintaining the temperature <20 °C. The organic layer was separated and filtered through silica gel (4 kg), and the filtrates containing the product were concentrated to 8.88 kg. ^{1}H NMR of the solution showed the material was 56.7 wt %, yielding 5.01 kg of allyl carbonate **21** (76% yield). Silica gel chromatography of a small sample yielded pure **21** as a light yellow oil). R_f 0.37 (hex: EtOAc = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 7.8, 5.9 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.09 (d, J = 9.6 Hz, 1H), 7.00−7.15 (m, 1H), 6.09−5.97 (m, 2H), 5.30−5.40 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J_{CF} = 241 Hz), 154.9, 140.8, 135.2, 130.2 (d, J_{CF} = 10.1 Hz), 122.6, 118.0, 115.3 (d, J_{CF} = 20.1 Hz), 113.9 (d, J_{CF} = 20.1 Hz), 79.3, 54.9. IR (neat, cm^{-1}) 2959, 1748, 1593, 1489, 1442. Anal. Calcd for $C_{11}H_{11}O_3F$: C, 62.85; H, 5.27. Found: C, 62.78; H, 5.32.

Methyl (5*S*)-2-Diazo-5-(3-fluorophenyl)-3-oxo-6-heptenoate (24). A 100-L flask equipped with mechanical stirrer, thermocouple, addition funnel, and nitrogen inlet was charged with **2** (94.63 kg, 18.5 mol), 1,2-dichloroethane (20 L), and 4-acetomidobenzenesulfonyl azide (4.40 kg, 18.3 mol). To this was added triethylamine (7.74 L, 55.5 mol) while maintaining the temperature <25 °C. The reaction was stirred at 20−25 °C for 4 h and filtered. The collected solid was washed with 1,2-dichloroethane (20 L). The combined 1,2-dichloroethane solutions was cooled to 5 °C and washed with 2 N HCl (14.4 L) and twice with H_2O (12.5 L). The organic layer was dried over $MgSO_4$, filtered, and used directly in the next reaction (4.88 kg, HPLC assay yield: 95%). Silica gel chromatography on a small sample yielded pure **24** as a colorless oil. R_f 0.52 (hex:EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.04 (d, J = 7.7 Hz, 1H), 6.97 (d, J = 10.1 Hz, 1H), 6.90 (m, 1H), 5.98 (ddd, J = 17.2, 10.4, 7.1 Hz), 5.08 (m, 2H), 4.02 (m, 1H), 3.85 (s, 3H), 3.67 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 190.3, 162.9 (d, J_{CF} = 247.4 Hz), 145.4 (d, J_{CF} = 7.2 Hz), 139.8, 129.9, (d, J_{CF} = 8.0 Hz), 123.4 (d, J_{CF} = 2.4 Hz), 115.2, 114.6 (d, J_{CF} = 20.9 Hz), 113.4 (d, J_{CF} = 20.1 Hz), 52.2, 44.8, 44.5. IR (neat, cm^{-1}) 2956, 2135, 1716, 1658, 1589. Anal. Calcd for $C_{14}H_{13}FN_2O_3$: C, 60.87; H, 4.74; N, 10.14. Found: C, 60.83; H, 4.72; N,10.10. The ee was determined to be 98%. HPLC ee analysis (ChiralPak AD-RH, 4.6 × 250 mm, flow rate = 0.5 mL/min, detection at 210 nm, H_2O:acetonitrile 20:80): t_R = 7.2 min (minor), t_R = 8.5 min (major).

Methyl (1*S*,4*S*,5*R*)-4-(3-Fluorophenyl)-2-oxobicyclo[3.1.0]hexane-1-carboxylate (29). A 100-L flask equipped with a 5-L addition funnel, reflux condenser, temperature probe, stopper, and overhead stirrer was charged with 1,2-dichloroethane (11 L) and $(CH_3CN)_4CuPF_6$ (55.41 g, 0.149 mol) and heated to 77 °C. To this was slowly added a 1,2-dichloroethane solution of **24** (1.38 kg, 5.0 mol, 2.5 L) over a period of 8 h, with the reaction temperature maintained between 77 and 81 °C. At the end of the addition, the reaction was stirred for an additional hour and then cooled to room temperature. Brine was added (30 L) and the organic layer was separated, dried over $MgSO_4$, and filtered. The filtrate was filtered through a silica gel pad and concentrated to give 1.20 kg of **29**/**30** (96.5% yield for the combined trans and cis products) in a ratio of 4.47:1 trans:cis. Silica gel chromatography on a small sample yielded pure **29** as a colorless oil. R_f 0.35(hex:EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.33 (m, 1H), 6.89−6.96 (m, 3H), 3.82 (s, 3H), 3.49 (d, J = 8.5 Hz, 1H), 2.76 (dd, J = 19.1, 8.5 Hz, 1H), 2.64 (m, 1H), 2.28 (d, J = 19.1 Hz, 1H), 2.13−2.17 (m, 1H), 1.54 (t, J = 5.3 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 205.5, 168.3, 163.1 (d, J_{CF} = 241 Hz), 147.1, 130.8 (d, J_{CF} = 10.1 Hz), 122.0, 114.1 (d, J_{CF} = 10.1 Hz), 113.6 (d, J_{CF} = 10.1 Hz), 52.7, 42.4, 39.0, 38.9, 38.0, 21.5. IR (neat, cm^{-1}) 1732, 1589, 1438. Anal. Calcd for $C_{14}H_{13}FO_3$ (5.5:1 mixture of **29**:**30**): C, 67.73; H, 5.28. Found: C 67.36; H, 5.26.



NOE's

Methyl (1*R*,4*S*,5*S*)-4-(3-Fluorophenyl)-2-oxobicyclo[3.1.0]hexane-1-carboxylate (30). Colorless oil. R_f 0.40 (hex: EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.36 (m, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.89−7.03 (m, 2H), 3.87 (m, 1H), 3.80 (s, 3H), 2.90−2.95 (m, 1H), 2.70 (dd, J = 18.3, 9.0 Hz, 1H), 2.35 (dd, J = 18.3, 10.5 Hz), 2.14−2.18 (m, 1H), 1.62 (t, J = 5.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.1, 168.2, 163.1 (d, J_{CF} = 246 Hz), 143.3 (d, J_{CF} = 10.1 Hz), 130.4 (d, J_{CF} = 10.1 Hz), 122.6, 114.1(d, J_{CF} = 10.1 Hz), 113.9 (d, J_{CF} = 10.1 Hz), 52.5, 39.8, 38.5, 37.3, 35.8, 20.6. IR (neat, cm^{-1}) 1732, 1589, 1438. Anal. Calcd for $C_{14}H_{13}FO_3$ (5.5:1 mixture of **29**:**30**): C, 67.73; H, 5.28. Found: C 67.36; H, 5.26

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[28] The absolute stereochemistry was assigned by analogy to the phenyl analogue. See ref 11c.