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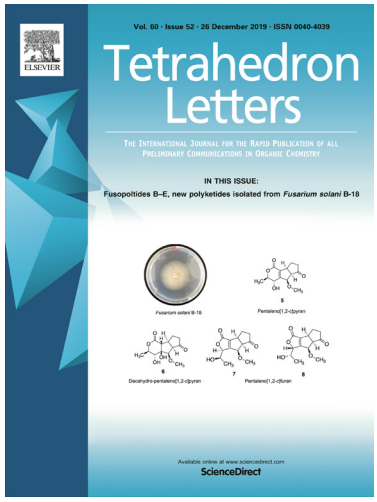

A Synthetic Protocol for (–)-Ketorolac; Development of Asymmetric Gold(I)-Catalyzed Cyclization of Allyl Alcohol with Pyrrole Ring Core

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PII: S0040-4039(19)31363-2
DOI: https://doi.org/10.1016/j.tetlet.2019.151564
Reference: TETL 151564

To appear in: *Tetrahedron Letters*

Received Date: 16 November 2019
Revised Date: 20 December 2019
Accepted Date: 23 December 2019

Please cite this article as: Sasaki, I., Yamasaki, N., Kasai, Y., Imagawa, H., Yamamoto, H., A Synthetic Protocol for (–)-Ketorolac; Development of Asymmetric Gold(I)-Catalyzed Cyclization of Allyl Alcohol with Pyrrole Ring Core, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151564

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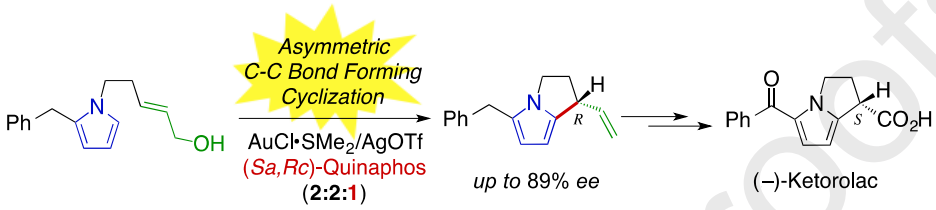

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A Synthetic Protocol for (–)-Ketorolac; Development of Asymmetric Gold(I)-Catalyzed Cyclization of Allyl Alcohol with Pyrrole Ring Core

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Keyword_1 *Ketorolac*
Keyword_2 *Enantioselective synthesis*
Keyword_3 *Allyl alcohol cyclization*
Keyword_4 *Gold(I) catalyst*

ABSTRACT

An asymmetric synthesis of (–)- and (+)-ketorolac was achieved with 89% *ee* using a novel Friedel–Crafts (FC) type C-C bond forming cyclization of an allyl alcohol containing a pyrrole ring core in the presence of a bimetallic gold(I) salt complex prepared from a 2:2:1 combination of AuCl·SMe_2, AgOTf and chiral Quinaphos.

1. Introduction

Ketorolac (±)-**1**, which acts as a cyclooxygenase (COX) inhibitor, is a well-known racemic non-steroidal anti-inflammatory drug (NSAID) used all over the world. However, it has been demonstrated experimentally that only (–)-**1** shows a significantly high level of anti-inflammatory activity, while (+)-**1** is ineffective.[1] There is sometimes a marked difference in the biological efficacy of enantiomers, and it not unusual to observe that only one enantiomer of a racemate displays a desired medicinal property. Accordingly, in the field of drug discovery, significant efforts have been devoted to develop enantiopure drugs with the aim of enhancing beneficial efficacies and/or eliminating side effects.[2]

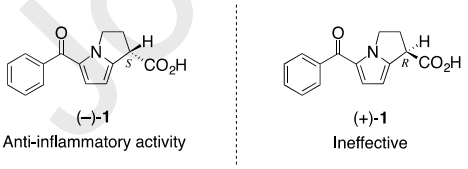
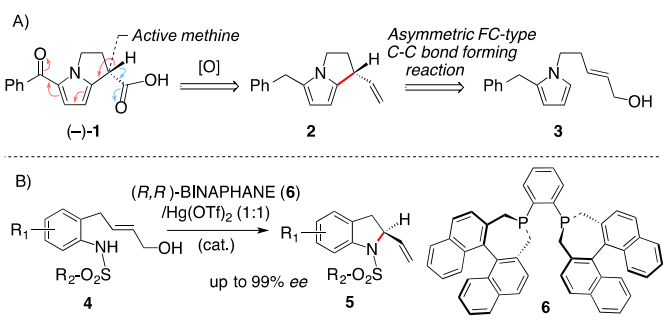


Figure 1. The stereochemistry of ketorolac (**1**)

Herein, we describe an enantioselective synthesis of (–)-**1** using a novel asymmetric Friedel–Crafts (FC) type cyclization of a pyrrolic allyl alcohol with a bimetallic gold(I) salt complex, which was prepared from a 2:2:1 combination of AuCl·SMe_2, AgOTf and (*Sa*,*Rc*)-Quinaphos. Nearly 30 years have passed since (±)-**1** was approved as a medical drug. However, an asymmetric synthesis of (–)-**1** has scarcely been developed to date, except for some methods using enzymatic resolutions of (±)-**1** and the related racemic intermediates.[3,4] In 2005, the Baran group reported an enantioselective synthesis of (–)-**1** having 90% *ee* on the basis of an attractive synthetic strategy that featured an asymmetric direct coupling of unfunctionalized C(sp^2) and C(sp^3) atoms.[5]

2. Result and discussion

The heart of our synthetic plan is illustrated in scheme 1A. The sole chiral center of (–)-**1**, which is located between a benzoyl pyrrole and carboxyl group, is labile under many reaction conditions via keto–enol tautomerism. Thus, the 2-benzyl pyrrole derivative **2** was designed as a key intermediate that could be converted to **1** by an oxidation reaction in the last stage of the total synthesis.



Scheme 1. A) Our synthetic plan of (–)-**1**. B) Asymmetric C-N bonding cyclization of anilino allyl alcohol **4**

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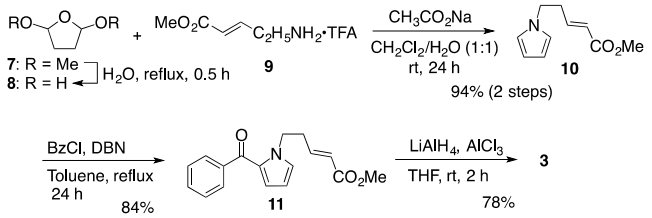
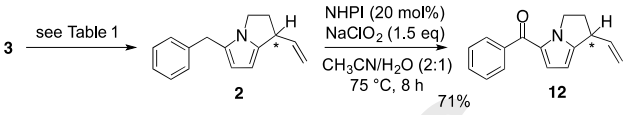
O ...out type cyclization of pyrrolic allyl alcohol **3** in an enantioselective manner. Recently, our group developed an asymmetric C-N bond forming cyclization of anilino allyl alcohol **4** with a 1:1 combination of a $Hg(OTf)_2$ catalyst and the chiral ligand BINAPHANE (**6**) (Scheme 1B).[6] Therefore, we anticipated that optically active **2** could be prepared from **3** using the same reaction conditions or conceptually similar reactions.



Scheme 2. Preparation of pyrrolic allyl alcohol derivative **3**

The cyclization precursor **3** was prepared from commercially available 2,5-dimethoxytetrahydrofuran (**7**) and a trifluoroacetate salt of methyl (*E*)-5-aminopent-2-enoate (**9**) (Scheme 2). Initially, **7** was hydrolyzed to give the 2,5-diol derivative **8** in isolation, was reacted with **9** in the presence of a sodium acetate buffer.[7] At room temperature with exclusion from light, the desired Clauson-Kaas type reaction gradually proceeded, giving the *N*-substituted pyrrole **10** in 94% yield after 24 hours.[8] Next, regioselective *C*2-acylation of **10** with benzoyl chloride was carried out using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in toluene under reflux conditions, and then the resulting **11** was treated with $LiAlH_4$ in the presence of $AlCl_3$ to give **3** as a single regioisomer.[9]

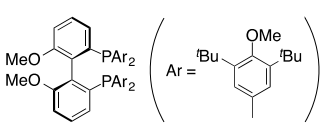


Scheme 3. The asymmetric cyclization of **3** and then the oxidation reaction to form benzoyl pyrrole derivative **12**

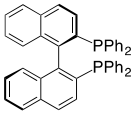
Subsequently, an FC-type cyclization of **3** towards **2** was tried (Scheme 3). The details of the reaction conditions are described in Table 1.

Table 1. Optimization of the asymmetric FC-type cyclization of **3** towards **2**[a]

Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Temp.	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	$Hg(OTf)_2$ (10)	(*R*,*R*)-**6** (10)	Toluene	rt	24	0 (40)[d]	-
2	$Hg(OTf)_2$ (20)	(*R*,*R*)-**6** (10)	Toluene	rt	24	0 (9)[d]	-
3	$Hg(OTf)_2$ (10)	(*R*,*R*)-**6** (20)	Toluene	rt	24	0 (48)[d]	-
4	$Hg(OTf)_2$ (20)	(*R*,*R*)-**6** (20)	Toluene	rt	24	0 (31)[d]	-
5	$Hg(OTf)_2$ (20)	(*R*,*R*)-**6** (20)	Toluene	reflux	24	0 (7)[d]	-
6	AuCl·SMe_2/AgOTf (20)[e]	(*R*,*R*)-**6** (10)	Toluene	rt	24	20 (65)[d]	69
7	AuCl·SMe_2/AgOTf (20)[e]	(*R*)-**13** (10)	Toluene	rt	24	0 (95)[d]	-
8	AuCl·SMe_2/AgOTf (20)[e]	(*R*)-**13** (10)	Toluene	reflux	24	28 (30)[d]	3
9	AuCl·SMe_2/AgOTf (20)[e]	(*R*)-**14** (10)	Toluene	rt	24	0 (92)[d]	-
10	AuCl·SMe_2/AgOTf (20)[e]	(*S*,*S*)-**15** (10)	Toluene	rt	24	0 (>95)[d]	-
11	AuCl·SMe_2/AgOTf (20)[e]	(*R*,*R*)-**16**(10)	Toluene	rt	24	0 (>95)[d]	-
12	AuCl·SMe_2/AgOTf (20)[e]	(*R*,*R*)-**17** (10)	Toluene	rt	24	trace (70)[d]	-
13	AuCl·SMe_2/AgOTf (20)[e]	(*Sa*,*Rc*)-**18** (10)	Toluene	rt	24	15 (80)[d]	–86
14	AuCl·SMe_2/AgOTf (20)[e]	(*Sa*,*Rc*)-**18** (10)	THF	rt	24	0 (95)[d]	-
15	AuCl·SMe_2/AgOTf (20)[e]	(*Sa*,*Rc*)-**18** (10)	CH_3NO_2	rt	24	0 (70)[d]	-
16	AuCl·SMe_2/AgOTf (20)[e]	(*Sa*,*Rc*)-**18** (10)	CH_2Cl_2	rt	24	25 (70)[d]	–88
17	AuCl·SMe_2/AgOTf (20)[e]	(*Sa*,*Rc*)-**18** (10)	CH_2Cl_2	rt	72	34 (50)[d]	–86
18	AuCl·SMe_2/AgOTf (20)[e]	(*Sa*,*Rc*)-**18** (10)	CH_2Cl_2	reflux	72	20 (34)[d]	< –54
19	AuCl·SMe_2/AgOTf (30)[e]	(*Sa*,*Rc*)-**18** (15)	CH_2Cl_2	rt	72	52 (32)[d]	–87
20	AuCl·SMe_2/AgOTf (40)[e]	(*Sa*,*Rc*)-**18** (20)	CH_2Cl_2	rt	72	72 (0)[f]	–89
21	AuCl·SMe_2/AgOTf (20)[e]	(*Sa*,*Rc*)-**18** (20)	CH_2Cl_2	rt	72	13 (67)[d]	–63

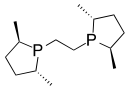


(*R*)-2,5-*t*Bu$_2$-4-MeO-MeObisphosphine (**13**)

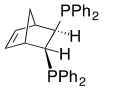


(*R*)-BINAP (**14**)

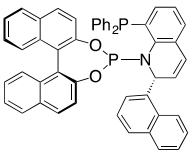
(*S*,*S*)-CHIRAPHOS (**15**)



(*R*,*R*)-Me-BPE (**16**)



(*R*,*R*)-NORPHOS (**17**)



(*Sa*,*Rc*)-QUINAPHOS (**18**)

[a] Reactions were run on a 0.1 mmol scale of **3** at a concentration of 0.01 M with exclusion from light under an argon atmosphere.

[b] Isolated yield of purified **2**.

[c] Enantiomeric excess of purified **12**. See supplementary file for further details.

[d] Recovery (%) of starting material **3**.

[e] AuCl·SMe_2 and AgOTf were mixed in a 1:1 ratio.

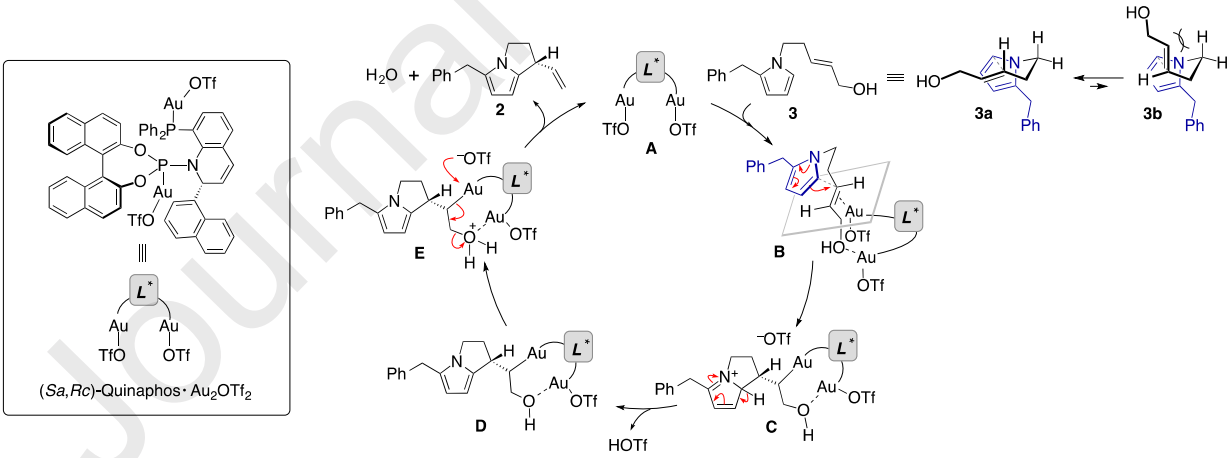
[f] 0.4 mmol of **3** was used in order to synthesize (–)-**1**. The cyclization was carried out with a 2:2:1 combination of AuCl·SMe_2, AgOTf and (*Sa*,*Rc*)-**18**.

combination of $Hg(OTf)_2$ and (*R*,*R*)-**6** that was developed in our laboratory for an asymmetric C-N bond forming cyclization of anilino allyl alcohol. At first, the use of 10 mol% of $Hg(OTf)_2$ and (*R*,*R*)-**6** was tried (Entry 1). However, the desired cyclization was very difficult and starting material **3** was recovered in 40% yield along with complex mixtures not containing **2**. Reaction conditions were attempted changing the ratio of $Hg(OTf)_2$ and (*R*,*R*)-**6** to 2:1 and 1:2 (Entries 2 and 3), but **2** was not formed and **3** remained in either case. Even under reflux conditions in the presence of 20 mol% of $Hg(OTf)_2$ and the chiral auxiliary, **3** was still recovered and the cyclic product was not detected (Entries 4 and 5). Thus, we decided to explore more suitable conditions for the FC-type cyclization of **3**.

In 2009, Bandini and co-workers reported a conceptually similar C-C bond forming cyclization of allyl alcohols with an indole ring core in the presence of a 2:2:1 combination of $AuCl{\cdot}SMe_2$, AgOTf and 2,5-*t*Bu_2-4-MeO-MeObisphosphine **13**.[10] These reaction conditions catalytically induced asymmetric cyclization to give the corresponding six-membered ring products (1- and 4-vinyl-tetrahydrocarbazole derivatives) with high enantioselectivity. In the successful FC-type reactions, a cationic gold(I) salt, which was prepared by mixing $AuCl{\cdot}SMe_2$ and AgOTf, played a significant role in the activation of the allyl alcohol moiety in the adduct, facilitating alkylation of the indole ring core and then the release of H_2O. Thus, we tried using the combination of $AuCl{\cdot}SMe_2$ and AgOTf instead of $Hg(OTf)_2$. Initially, 20 mol% of $AuCl{\cdot}SMe_2$ and AgOTf was examined. (*R*,*R*)-BINAPHANE (10 mol%) was used as the chiral auxiliary (Entry 6). When the reaction was carried out in toluene at room temperature, the desired cyclization proceeded slightly, giving a desired 5-*exo*-*trig* type product **2** in 20% yield after 24 hours.[11] Although 65% of starting material was recovered, it was obvious that the combination of $AuCl{\cdot}SMe_2$ and AgOTf was more effective than $Hg(OTf)_2$ (Entry 2 vs 6). We attempted to measure the enantiomeric excess of the resulting product **2**; however, columns, we could not separate the enantiomers. Therefore, **2** was treated with *N*-hydroxyphthalimide (NHPI) and $NaClO_2$ to give the benzoyl pyrrole derivative **12**,[12] and 69% *ee* was determined by chiral HPLC.[13] After obtaining this positive result that optically enriched **2** was formed in an FC-type cyclization of **3**,[14] we explored finding a more suitable chiral auxiliary for the asymmetric cyclization.

Unexpectedly, 2,5-*t*Bu_2-4-MeO-MeObisphosphine **13**, which has been utilized for the asymmetric cyclization of allyl alcohols containing an indole ring core, gave no product at room temperature (Entry 7). Under reflux for 24 hours, the desired FC-type cyclization of **3** proceeded somewhat, but the product was nearly racemic (Entry 8). BINAP **14**[15a], CHIRAPHOS **15**[15b], Me-BPE **16**[15c], NORPHOS **17**[15d] also gave a similar result as **13**, and either none or a trace amount of **2** was produced (Entries 9-12). In terms of chiral induction, (*Sa*,*Ra*)-Quinaphos **18**[16] furnished the best result, 86% *ee* (Entry 13). However, the chemical yield from **3** to **2** was only 15%. Thus, in order to improve the conversion efficiency, optimization was tried as shown in Entries 14-21. Consequently, it was found that CH_2Cl_2 was the best solvent of choice (Entry 16), and eventually a 72% yield was achieved by using a double dose of $AuCl{\cdot}SMe_2$ (40 mo%), AgOTf (40 mo%) and **18** (20 mo%) in CH_2Cl_2 at room temperature for 72 hours (Entry 20). The resulting product **2** was transformed to **12**, and an 89% *ee* was determined.

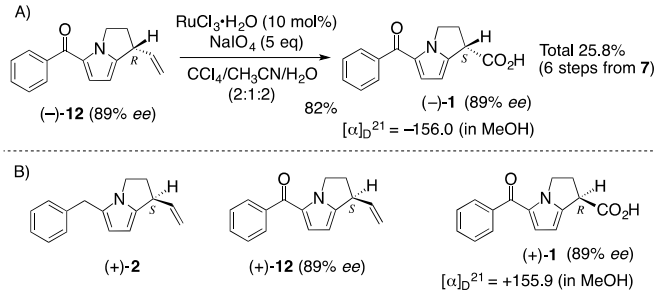
As described above, we managed to prepare **2** with 89% *ee* by using the FC-type cyclization of **3** with a 2:2:1 combination of $AuCl{\cdot}SMe_2$, AgOTf and **18**. Although an intensive search is required to demonstrate the reaction mechanism completely, we postulate that the bimetallic structure of the gold complex (*Sa*,*Rc*)-Quinaphos·Au_2OTf_2, which was formed by mixing $AuCl{\cdot}SMe_2$, AgOTf and **18** in a 2:2:1 ratio, probably contributes to the progress of the reaction smoothly as well as asymmetric induction.



Scheme 4. Proposed mechanism of FC-type cyclization of **3** with a bimetallic gold(I) catalyst.

As shown in Scheme 4, one gold salt in the formed bimetallic gold complex **A** initiates the alkylation of the pyrrole ring core by activating the allylic C-C double bound in adduct **3**. At the point of nucleophilic attack from the pyrrole ring core, two plausible conformers **3a** and **3b** are plausible. However, the reaction dominantly proceeds through conformer **3a** that offers minimal 1,3-diaxial interactions after the gold complex chooses the reaction surface. In contrast, another gold salt in complex **A** chelates to the hydroxyl group in **3**, and then induces β-hydroxy elimination in cooperation with the HOTf that was generated through the aromatization of the 2*H*-pyrrolium intermediate **C** to **D**. The experimental finding that the monometallic condition with a 1:1:1 combination of $AuCl{\cdot}SMe_2$, AgOTf and **18** drastically decreased the chemical yield of **2** as well as chiral induction (Entries 21 vs 17) suggests that the bimetallic structure of **A**, which has a function capable of activating both of double bond and the hydroxy group, is pivotal in facilitating the FC-type cyclization.

Finally, optically enriched ketorolac (–)-**1** was synthesized from (–)-**12** with 89% *ee* in 82% yield. The *ee* was not diminished by treatment with $RuCl_3 \cdot H_2O$ (10 mol%) and $NaIO_4$ (5 equiv) at 0 °C in a 2:1:2 mixed solvent of CCl_4, CH_3CN and H_2O (Scheme 5A).[17] The ^1H and ^{13}C NMR spectral data of synthetic (–)-**1** correspond well to those previously reported in the literature.[5] With the established successful pathway to (–)-**1**, its enantiomer (+)-**1** having 89% *ee* was also synthesized from (+)-**12**, which was prepared using (*Ra*,*Sa*)-Quinaphos as the chiral auxiliary in an asymmetric cyclization of **3** (Scheme 5B). Naturally, the optical rotations of synthetic (–)-**1** and (+)-**1** were close in magnitude, but of opposite sign. Because the absolute stereochemistry of (–)-**1** and (+)-**1** is equivalent to (*S*)- and (*R*)-ketorolac, respectively, these findings demonstrate that the FC-type cyclization of **3** with (*Sa*,*Ra*)-Quinaphos afforded the *R*-isomer of **2**, and (*Ra*,*Sa*)-Quinaphos gave the opposite stereochemistry to that shown.



Scheme 5. A) Oxidation of (–)-**12** leading to (–)-**1**. B) The structure of synthetic (+)-**2**, (+)-**12** and (+)-**1**.

In conclusion, we have developed a novel asymmetric C-C bond forming cyclization of pyrrolic allyl alcohol **3** with a 2:2:1 combination of $AuCl \cdot SMe_2$, AgOTf and chiral Quinaphos, which was successfully applied to the asymmetric synthesis of ketorolac. Using (*Sa*,*Ra*)-Quinaphos as the chiral auxiliary, cyclic (*R*)-**2** was obtained as a key intermediate for the synthesis of (*S*/–)-ketorolac. The synthetic procedure (25.8% overall yield and in 6 steps from a commercially available **7**) facilitates the development of enantiopure (–)-ketorolac and investigations into the latent biological properties of (–)- and (+)-ketorolac.

Acknowledgments

We are grateful to Dr Yasuko Okamoto (analysis center in Tokushima Bunri University) for determining the HRMS. This study was financially supported by a Grant-in-Aid (No. 23790034) from the MEXT (Ministry of Education, Culture, Sports, Science, and Technology) of the Japanese Government.

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14. The cyclization of 2-benzoyl pyrrole derivative towards **12** was also examined. However, the cyclization didn't proceed using a 2:2:1 combination of $AuCl \cdot SMe_2$, AgOTf and **18**. For further details, see supplementary file.
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Supplementary Material

Supplementary data to this article can be found online.

Hig

- An enantioselective synthesis of ketorolac was achieved with 89% ee.
- An asymmetric allyl alcohol cyclization was developed as a key reaction.
  A gold(I) catalyst facilitated the allyl alcohol cyclization.