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A practical asymmetric conjugate addition to cyclic enones with chiral bifunctional Ru amido catalysts

Pavel A. Dub, Hui Wang, Masahito Watanabe, Ilya D. Gridnev, Takao Ikariya *

Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, 2-12-1-E4-1 O-okayama, Meguro-ku, Tokyo 152-8552, Japan

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ABSTRACT

A practical asymmetric C–C bond formation to synthetically useful β-chiral cyclic ketones (>99% ee) using bifunctional chiral amido Ru catalysts under an S/C = 1000, the highest ratio achieved so far in the literature for this class of reactions, is described. The catalytic reactivity decreases in the order of Ru(Msdpen)(hmb) > Ru(Pfbsdpen)(hmb) > Ru(Tsdpen)(hmb) > Ru(PMsdpen)(hmb), where Ru(Pfbsdpen)(hmb) is a newly developed chiral bifunctional catalyst. Complex Ru(Msdpen)(hmb) was identified as the best in terms of reactivity and enantioface selectivity, whereas Ru(PMsdpen)(hmb) gave unsatisfactory results. An importance of the NH proton in the bifunctional catalyst for determining the enantioselectivity has been experimentally demonstrated. Valuable information for the reaction mechanism was accumulated.

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Development of practical homogeneous transition metal-based chiral catalysts to access chiral compounds remains a significant challenge of synthetic organic chemistry.[1] Although a great variety of chiral molecular catalysts for practical asymmetric reduction of olefins and ketones have been developed during the last two decades,[2] only a limited number of chiral molecular catalysts for asymmetric C–C bond formation with an excellent stereoselectivity, reactivity, and low catalyst loading as well as operational simplicity have been reported.[3]

β-Chiral cyclic ketones are used as building blocks in preparation of natural products.[4] One possibility to construct this skeleton is asymmetric C–C bond formation through the Michael addition of a C-nucleophile to α,β-unsaturated cyclic enones. Organoelement-,[5] organo-,[6] polymer-supported,[7] and nanocatalysts[8] were widely employed for such reactions. Although there have been many chiral catalysts showing good to excellent enantioselectivities, typical loadings of the catalysts were usually very high, typically with a substrate/catalyst molar ratio (S/C) of 5–10 except for Morris ruthenium catalyst.[5b]

Recently, we have successfully applied originally developed asymmetric transfer hydrogenation catalysts, Ru(*N*-sulfonylated dpen)(η^6-arene), (**1**, DPEN: 1,2-diphenylethylenediamine) to asymmetric conjugate addition reactions of 1,3-dicarbonyl compounds to cyclic enones and nitroalkenes.[9] This bifunctional catalysis provides a wide substrate scope and high practicability, producing the desired chiral adducts in almost quantitative yields. After separation of the catalyst by simple flash chromatography followed by evaporation of the eluent, the chiral products with >99% ee can be obtained.[9]

However, a drawback in this catalysis was relatively high catalyst loading (S/C = 50) for the completion of the reaction at room temperature even with the best catalyst, Ru((*R*,*R*)-*N*-sulfonylated dpen)(hmb) (hmb = hexamethylbenzene).[9]

Here we report that the Msdpen complex **1a** and a newly developed chiral Ru complex **1d** are capable to perform the asymmetric conjugate addition at S/C = 1000 leading to the desired chiral ketone with excellent ee's >99% as shown in Scheme 1. Moreover, tuning of the catalyst structure and reaction conditions resulted in a useful protocol for practical synthesis of chiral cyclic ketones from 2-cyclopentenone. Additionally, we provide experimental evidence for the crucial importance of the presence of NH protons in the bifunctional catalyst and the solvent polarity for the enantioselective reaction.

The outcome of the conjugate addition was found to be highly influenced by the structure of the catalysts, Ru((*R*,*R*)-*N*-sulfonylated dpen)(η^6-arene).[9] In particular, in contrast to the trend of the reactivity for the asymmetric transfer hydrogenation, the TsDPEN complexes bearing the electron-donating and structurally congested hexamethylbenzene ligand exhibited the best catalytic performance in terms of selectivity and reactivity. The reaction of cyclic enones (**2a**,**b**) and malonate **3a** or β-keto ester **3b** with a 1:1 molar ratio and the S/C = 50 in *tert*-butyl alcohol containing the catalyst **1a** proceeded smoothly to give the corresponding Michael adducts **4a** or **4b** with excellent ee's and yields as listed in Table 1 (and Supplementary data). *tert*-Butyl alcohol was the best solvent for the reaction with

* Corresponding author. Tel.: +81 3 5734 2636; fax: +81 3 5734 2637.
E-mail address: tikariya@apc.titech.ac.jp (T. Ikariya).

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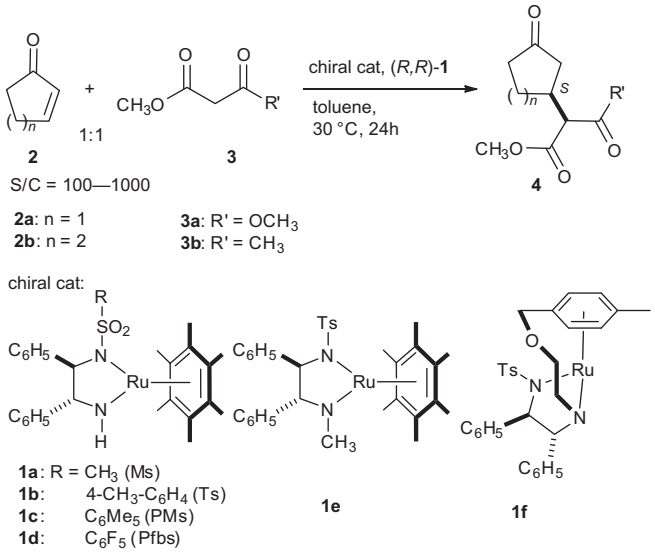


Scheme 1. Asymmetric C–C bond formation with chiral amido catalysts.

Table 1
Asymmetric Michael reactions of enones and dimethylmalonate or methyl acetoacetate catalyzed by chiral (*R*,*R*)-Ru amido complexes[a]

Run	Enone	Donor	Catalyst	Solvent	S/C	Yield[b] (%)	ee[c] (*S*) (%)
1	**2a**	**3a**	—	Toluene		0	
2	**2a**	**3a**	**1a**	^{t}BuOH	50[d]	99[e]	>99
3	**2a**	**3a**	**1a**	^{t}BuOH	100	100	92
4	**2a**	**3a**	**1a**	^{t}BuOH	500	100	86
5	**2a**	**3a**	**1a**	^{t}BuOH	1000	100	84
6	**2a**	**3a**	**1a**	Toluene	50	100	>99
7	**2a**	**3a**	**1a**	Toluene	100	100	>99
8	**2a**	**3a**	**1a**	Toluene	500	100	>99
9	**2a**	**3a**	**1a**	Toluene	1000	97	>99
10	**2a**	**3a**	**1a**	Toluene	2000	56	>99
11	**2a**	**3a**	**1b**	Toluene	50	100	>99
12	**2a**	**3a**	**1b**	toluene	1000	35	98
13	**2a**	**3a**	**1c**	Toluene	1000	7	60
14	**2a**	**3a**	**1d**	Toluene	50	100	90
15	**2a**	**3a**	**1d**	Toluene	100	100	96
16	**2a**	**3a**	**1d**	Toluene	500	86	98
17	**2a**	**3a**	**1d**	Toluene	1000	70	99
18	**2b**	**3a**	**1a**	Toluene	500	42[f]	98
19	**2b**	**3a**	**1a**	Toluene	1000	26[f]	>99
20	**2a**	**3b**	**1a**	Toluene	500	85	96[g]
21	**2a**	**3b**	**1a**	Toluene	1000	27	91[g]
22	**2a**	**3a**	**1e**	^{t}BuOH	50[d]	>99	8
23	**2a**	**3a**	**1f**	Toluene	500	70	4
24	**2a**	**3a**	**1b**	Ionic liquid	100[h]	92	0
25	**2a**	**3a**	**1d**	Ionic liquid	500[h]	26	0

[a] Unless otherwise noted, the reactions were carried out using 1.0 mmol of Michael acceptors and donors (1:1) in 1.0 mL of toluene (30 °C, 24 h).
[b] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard, see SI.
[c] Determined by HPLC analysis (see SI), (*S*) = config.
[d] At 40 °C.
[e] Isolated yield after flash chromatography on the silica gel, data from.[9]
[f] In 48 h.
[g] Obtained as a 1:1 mixture of diastereomers with a single stereogenic center on cyclopentanone ring.
[h] Ionic liquid = 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)-imide.

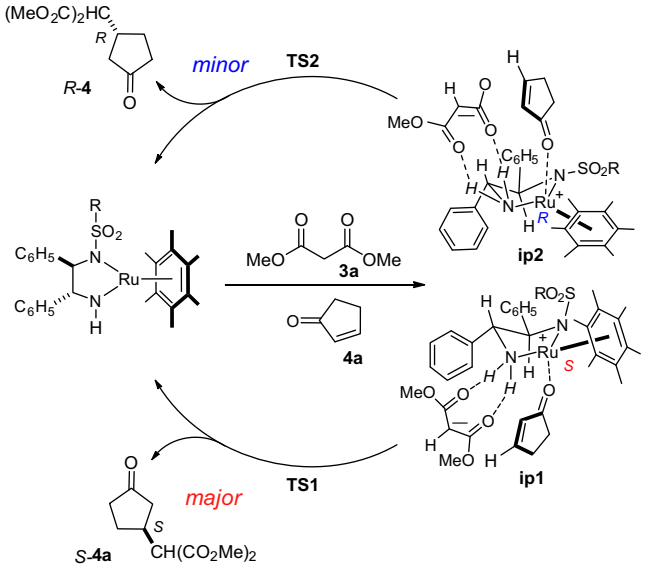
S/C = 50. However, an increase in the S/C from 50 to 500 or 1000 for the model reaction of **2a** and **3a** resulted in the serious decrease in the ee value to 86 and 84%, respectively (runs 2–5). Contrary to this trend, the use of toluene as a non-polar solvent, caused almost complete conversion with S/C = 500 and 1000, giving the product with >99% ee (runs 6–9).

The reaction with S/C = 2000 using **1a** afforded compound **4a** with an excellent ee (>99%) but only in a moderate yield (run 10). The resulting chiral cyclic ketone **4a** is an important intermediate in methyl jasmonate synthesis.[10]

Notably, usually well-performing complex **1b** bearing TsDPEN ligand gave unsatisfactory results in terms of reactivity (runs 11,12), and the complex **1c** having a sterically congested pentamethylbenzene sulfonylated DPEN (PMsDPEN) gave poor catalytic performance in this reaction with S/C = 1000 (run 13).

These results prompted us to modify the structure of the substituent at the SO_2 group for further improvement of the catalytic performance. We prepared a new Ru catalyst **1d** that proved to be effective for the asymmetric conjugate addition of 1,3-dicarbonyl compounds to cyclic enones even with S/C = 1000, giving the chiral adduct with an excellent ee (runs 14–17). Thus, the reaction of 2-cyclopentenone **2a** with **3a** in toluene catalyzed by the catalyst **1a** or **1d** at S/C = 1000 gave the chiral adduct **4a** with excellent enantioselectivity (>98% ee) in a reasonably good yield. The reaction of 2-cyclohexanone (**2b**) and **3a** or the reaction of **2a** with β-keto ester (**3b**) gave with low catalyst loadings excellent ee's, but unsatisfactory yields (runs 18–21).

Recently we proposed a possible mechanism for the asymmetric Michael addition of 1,3-dicarbonyls to cyclic enones based on NMR and computational analyses.[9d] According to this mechanism, a key intermediate in this catalytic reaction is the chelating contact ion paired ternary complex (**ip1** or **ip2**) stabilized by two hydrogen bonds to the NH_2 group as shown in Scheme 2. For the (*R*,*R*)-chiral *N*-sulfonylated DPEN catalyst, major *S*-enantiomer can be obtained *via* the TOF-determining transition state[11] having λ-configurated 5-membered ring with *S*-configurated metal[12] atom (TS1, *S-pathway*), whereas the formation of minor *R*-enantiomer occurs via the TOF-determining transition state having *δ*-configurated 5-membered ring with *R*-configurated metal atom (TS2, *R-pathway*).



amido catalyst	1a	1b	1c	1d
ΔG_{298K}/kcal-mol^{-1}	8.3	6.7	3.4	6.5

Scheme 2. Sense of the enantioselection within the proposed mechanism. Difference of the computed C-PCM free energies (298 K) of the *R*- and *S*-pathways, $\Delta G^{\circ\neq} = G(TS2)_{298\ K} - G(TS1)_{298\ K}$, kcal/mol^{-1}.

Formation of major *S*-enantiomer via complex having *R*-configurated metal atom and/or formation of minor *R*-enantiomer via complex having *S*-configurated metal atom were found much higher in energy.[9d] The bulkiness of the coordinated arene was identified as the main stereoregulating factor, and hexamethylbenzene complexes were found to give the best ee's.[9d]

In order to reinforce the reaction mechanism including the contact ion paired intermediates, we reevaluated computationally the transition states in toluene reaction field by expressing the bulk solvent effects through the conductor-like polarizable continuum model (C-PCM)[13] for both competing pathways for the Michael addition catalyzed by the catalysts studied in this work.

As can be seen from Scheme 2, for all complexes the computed difference in the C-PCM free energies of the transition states for *R*- and *S*-pathways is higher than 3.13 kcal/mol. This corresponds to the ee's over 99% for all studied reactions. Only the chiral catalysts **1a**, **1b**, and **1d** exhibit enantioseletivity in the range of those predicted by computations. Catalyst **1c** gives the product with 60% ee under all S/C ratios. Note that for this complex, the DFT calculations predict a smaller free energy difference for the two competing pathways than for the other catalysts.

Valuable information for the reaction mechanism of the asymmetric conjugate addition was provided by the reaction of **2a** with **3a** in the presence of complex **1e** bearing a methyl group on the amido nitrogen atom giving the product **4a** in almost quantitative yield but only with 8% ee (run 22). Similar result was obtained with oxo-tethered catalyst **1f**,[14] of 70% yield and 4% ee at S/C = 500 (run 23). Thus the catalysts bearing secondary amido groups gave the non-enantioselective catalytic reaction. This demonstrates the importance of having the NH_2 group for the formation of the corresponding transition states in the enantioselective pathway as shown in Scheme 2. The other catalytic pathways resulting in poor ee's might proceed via non-bifunctional activation.

Moreover, the reaction between **2a** and **3a** in the presence of **1b** in highly polar ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide produced racemic **4a** with 92% yield (run 24). This result can be explained by an impossibility to form ionic pairs stabilized by *two* hydrogen bonds in the polar solvent that eliminates the enantioselective pathway.

The structures of the theoretically found transition states for the enantioselective pathway (Scheme 2, Fig. 1) could help to understand the scope and limitations of the synthetic applicability of our method. In fact, the rate of the reaction between cyclic ketones and dimethylmalonate decreases dramatically in the order 2-cyclopentanone > 2-cyclohexanone as discussed above, that can be explained in view of the limited space available for the effective coordination of the substrate. In addition, an inactivity of less-rigid acyclic substrates can be also explained. No reaction occured between *E*-4-hexen-3-one or *E*-methyl crotonate with dimethylmalonate **2a** in the presence of **1a** (S/C = 100) at 30 °C. This result is in accord with the utmost importance of the fixed *S-trans* conformation of the enone unit for the formation of the transition states like TS1 or TS2. Conformational flexibility of the acyclic enones with preference to *S-cis* conformation may prevent the productive coordination of the substrate.

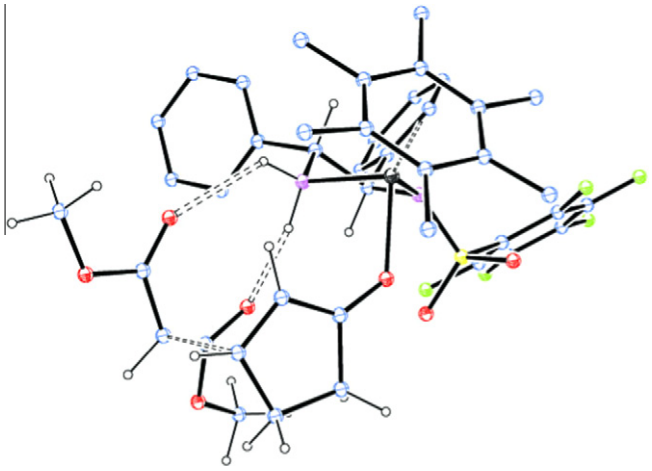


Figure 1. Optimized geometry of the transition state ($i269\ cm^{-1}$) for the reaction **2a** and **3a**, leading to *S*-enantiomer catalyzed by **1d** at B3LYP/SDD(Ru)/6-31G*(C,H,N,O,S,F)/C-PCM(toluene) level of theory. Some hydrogen atoms are omitted for clarity.

In conclusion, we have demonstrated a practical synthetic protocol for the production of synthetically useful β-chiral cyclic enones at low catalyst loadings with excellent ee's. Some additional insights into the mechanism of enantioselection were presented.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.100.

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