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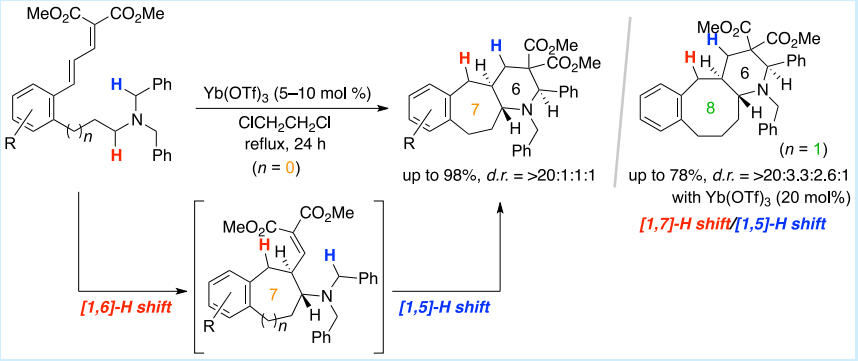
Highly Diastereoselective Synthesis of Medium-Sized Carbocycle-Fused Piperidines via Sequential Hydride Shift Triggered Double C(sp^3)−H Bond Functionalization

Miyabi Kataoka, Yuna Otawa, Natsuki Ido, and Keiji Mori*

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Nakacho, Koganei, Tokyo 184-8588, Japan

Supporting Information

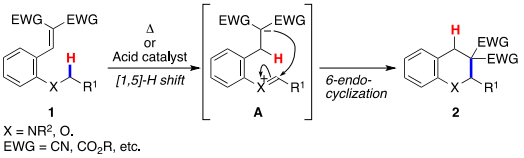


ABSTRACT: Herein we report a diastereoselective synthesis of medium-sized carbocycle-fused piperidines via [1,*n* (*n* = 6, 7)]-[1,5]-sequential hydride shift triggered double C(sp^3)−H bond functionalization. When cinnamylidene malonates having *N*,*N*-dibenzyl propylamine moiety were treated with 5 mol % of Yb(OTf)$_3$, a [1,6]-[1,5]-sequential hydride shift/cyclization process proceeded to afford seven-membered carbocycle-fused piperidines with excellent diastereoselectivities. This sequential system was applicable to the synthesis of eight-membered carbocycle-fused piperidines by an unprecedented [1,7]-[1,5]-sequential hydride shift/cyclization process.

The development of an efficient synthetic method that allows the construction of fused azacycles in a single operation is an important research topic because many useful organic molecules, such as biologically active compounds[1] and organocatalysts,[2] contain these skeletons. In particular, the synthesis of fused piperidines containing medium-sized rings, such as seven- and eight-membered carbocycles, which are also found in certain biologically active molecules,[1f] is a challenging task because even the construction of a single medium-sized ring is not a trivial issue. The difficulty lies in the large ring strain of medium-sized rings, and special caution such as the dropwise addition of a substrate is required to suppress competitive, unwanted intermolecular reactions.[3] The transition-metal-catalyzed cycloaddition reaction[4] and the intramolecular Diels−Alder reaction[5] are effective methodologies for the one-pot construction of the target skeletons; however, elegant achievements have been limited Therefore, the development of an effective synthetic method for medium-sized carbocycle-fused piperidines has been in great demand.

Our group has focused on the development of novel C(sp^3)−H bond functionalization that involves hydride shift triggered C(sp^3)−H bond functionalization, namely, the "internal redox process" (Scheme 1).[6−11] This reaction system has high synthetic utility; that is, various types of fused heterocycles can be constructed using this method. Quite recently, we achieved the sequential utilization of a [1,5]-hydride shift/cyclization process (double C(sp^3)−H bond functionalization),[11] which enables the highly diastereoselective synthesis of multisubstituted six-membered carbocycle-fused piperidines in a single operation (Scheme 2, upper part).[11a] Surprisingly, most of the internal redox reactions reported so far have focused on the formation of small rings, such as five- and six-membered rings. Their application to the construction of medium-sized rings (seven- or eight-membered rings) by a [1,*n* (*n* = 6, 7)]-hydride shift is quite limited,[12−14] although their intramolecular nature is expected to be suited

Scheme 1. C(sp^3)−H Bond Functionalization by Hydride Shift/Cyclization Process (Internal Redox Process)



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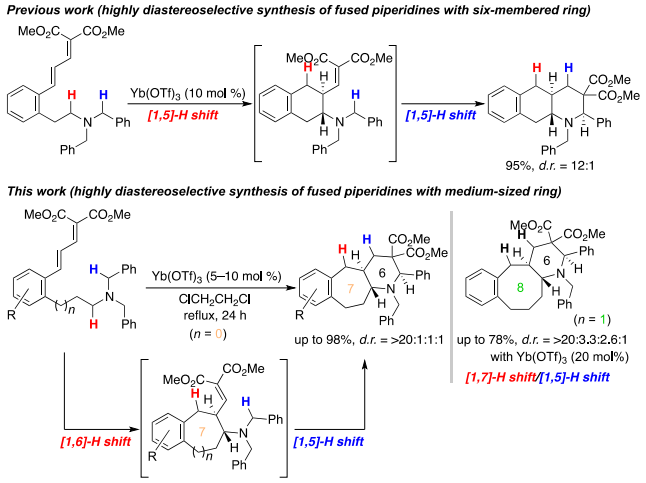
Scheme 2. Medium-Sized Carbocycle-Fused Piperidines via Sequential Hydride-Shift-Triggered Double C(sp^3)−H Bond Functionalization

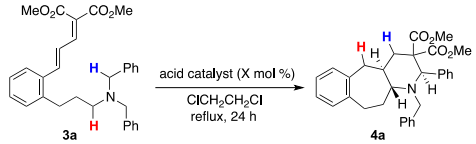


for the construction of medium-sized rings without special caution (such as dilution conditions). The combination of a [1,*n* (*n* = 6, 7)]-hydride shift and a [1,5]-hydride shift would open new doors to the synthesis of stereochemically defined medium-sized ring-fused piperidines in a single operation, which is otherwise difficult to achieve by the conventional method. Despite their high synthetic potential, to the best of our knowledge, there is no precedent for such kind of transformation.

Herein we report a highly diastereoselective synthesis of medium-sized carbocycle-fused piperidines via the above-mentioned strategy (Scheme 2, lower part). When cinnamylidene malonates having an *N*,*N*-dibenzyl propylamine moiety at the ortho position were treated with a catalytic amount of $Yb(OTf)_3$, the planned [1,6]-[1,5]-sequential hydride shift/cyclization process proceeded smoothly to afford seven-membered carbocycle-fused piperidines (7/6-fused ring system) in good chemical yield with excellent diastereoselectivities (up to 98%, d.r. = >20:1:1:1). We also found that this sequential system was applicable to the one-pot synthesis of synthetically challenging, eight-membered carbocycle-fused piperidines (8/6-fused ring system) by the [1,7]-[1,5]-sequential hydride shift/cyclization process.

The results of screening for the reaction conditions are summarized in Table 1. At first, a solution of cinnamylidene malonate **3a** in $ClCH_2CH_2Cl$ was treated with 10 mol % of $Sc(OTf)_3$, which exhibited excellent catalytic performance in most of the internal redox reactions we developed.[7] Gratifyingly, the planned [1,6]-[1,5]-hydride shift proceeded smoothly to give the desired seven-membered-ring-fused piperidine **4a** in good chemical yield (62%). It should be noted that the reaction proceeded in a highly stereoselective manner, and **4a** was obtained in the diastereomerically pure form (d.r. = >20:1:1:1), whose relative stereochemistry was unambiguously determined by X-ray analysis. To determine the most effective catalyst, an extensive screening for catalysts with focus on Lewis acid catalysts was conducted.[15] Although $Mg(OTf)_2$ and $Hf(OTf)_4$ promoted the reaction, the chemical yield of **4a** was low (<19%, entries 2 and 3). Inexpensive and commonly used Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3{\cdot}OEt_2$, were ineffective, and only the recovery of **3a** was observed (entries 4−6). In sharp contrast, $Gd(OTf)_3$ and

Table 1. Examination of the Reaction Conditions[a]



entry	catalyst	X	yield (%)[b] 4a	d.r.	3a
1	$Sc(OTf)_3$	10	62	>20:1:1:1	12
2	$Mg(OTf)_2$	10	19	>20:1:1:1	69
3	$Hf(OTf)_4$	10	11	>20:1:1:1	58
4	$TiCl_4$	10	0		68
5	$SnCl_4$	10	0		75
6	$BF_3{\cdot}OEt_2$	10	0		84
7	$Gd(OTf)_3$	10	55	>20:1:1:1	0
8	$Yb(OTf)_3$	10	72	>20:1:1:1	0
9	$Yb(OTf)_3$	5	84	>20:1:1:1	0
10[c]	$Yb(OTf)_3$	5	70	>20:1:1:1	0
11[d]	$Yb(OTf)_3$	5	74	>20:1:1:1	0
12[e]	$Yb(OTf)_3$	5	17	>20:1:1:1	70
13[f]	$Yb(OTf)_3$	5	0		65
14[g]	$Yb(OTf)_3$	5	0		71

[a]Unless otherwise noted, all reactions were conducted with 0.10 mmol of **3a** in the presence of an acid catalyst in $ClCH_2CH_2Cl$ (1.0 mL) at refluxing temperature. [b]Isolated yield. [c]Reaction was conducted at 0.50 M. [d]1.03 mmol scale. [e]In toluene. [f]In *o*-xylene. [g]In CH_3CN.

$Yb(OTf)_3$ promoted the reaction well, and good to high chemical yields were achieved (55 and 72%, respectively, entries 7 and 8). $Yb(OTf)_3$ was the catalyst of choice, and a satisfactory chemical yield (84%) was accomplished even with 5 mol % catalyst loading (entry 9). Notably, a high concentration reaction (0.50 M) afforded **4a** in good chemical yield with excellent diastereoselectivity (70%, with >20:1:1:1 entry 10). The scale-up reaction (1.03 mmol) resulted in the formation of **4a** without sacrificing the chemical yield (74%, entry 11). Screening for the solvent revealed that $ClCH_2CH_2Cl$ was the most effective solvent. Not only aromatic solvents such as toluene and *o*-xylene but also polar solvents (CH_3CN) resulted in low chemical yields (17% or lower, entries 12−14).

Next, the substrate scope of the present reaction was investigated (Figure 1). The reaction was applicable to substrates **3a**−**h** having electron-donating groups such as methyl and methoxy and an electron-withdrawing group (F) at various positions, and corresponding piperidine derivatives **4a**−**h** were obtained in good chemical yield with high to excellent diastereoselectivities. Tetracyclic product **4i** with a naphthalene core was obtained in satisfactory chemical yield and with satisfactory diastereoselectivity (98%, d.r. = >20:3.5:2.6:1). In contrast with the high tolerance of the substituents on the aromatic ring, there is the strong limitation of the substituents on the amine portion; that is, the *N*,*N*-dibenzylamine group was indispensable. Although substrate **3j** having an *N*,*N*-bis(4-chlorobenzyl)amine moiety afforded adduct **4j** in 63% yield, the desired adducts **4k** and **4l** were not obtained when substrates **3k** and **3l** with a methyl or an ethyl group in place of a benzyl group were employed. *N*,*N*-Diallyl substrate **3m** also did not afford the desired adduct **4m**. The relative stereochemistries of the major diastereomers were surmised, as shown in Figure 1, Schemes 2−4, and Table 1, by

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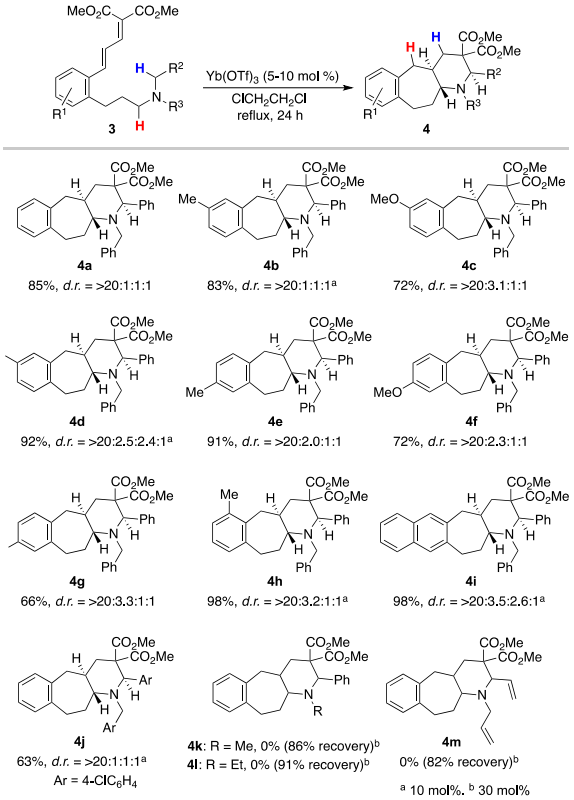


Figure 1. Substrate scope for [1,6]-[1,5]-hydride shift process.

analogy to **4a** and **4h**, whose relative stereochemistries were unambiguously established by X-ray crystallographic analysis.

Inspired by the excellent results of the [1,6]-[1,5]-hydride shift process, we turned our attention to the development of a more challenging [1,7]-[1,5]-hydride shift sequence for the formation of an 8/6-fused ring system (Figure 2). Although

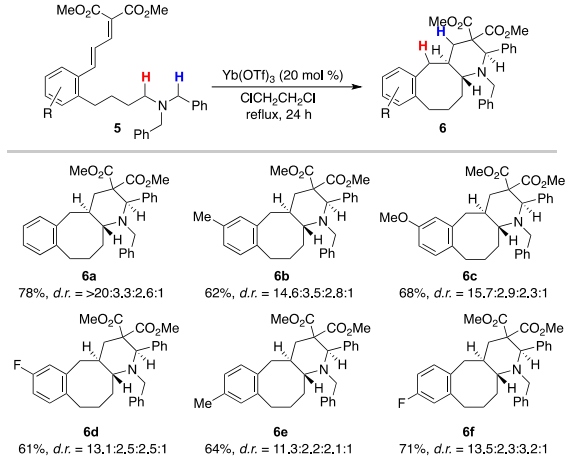
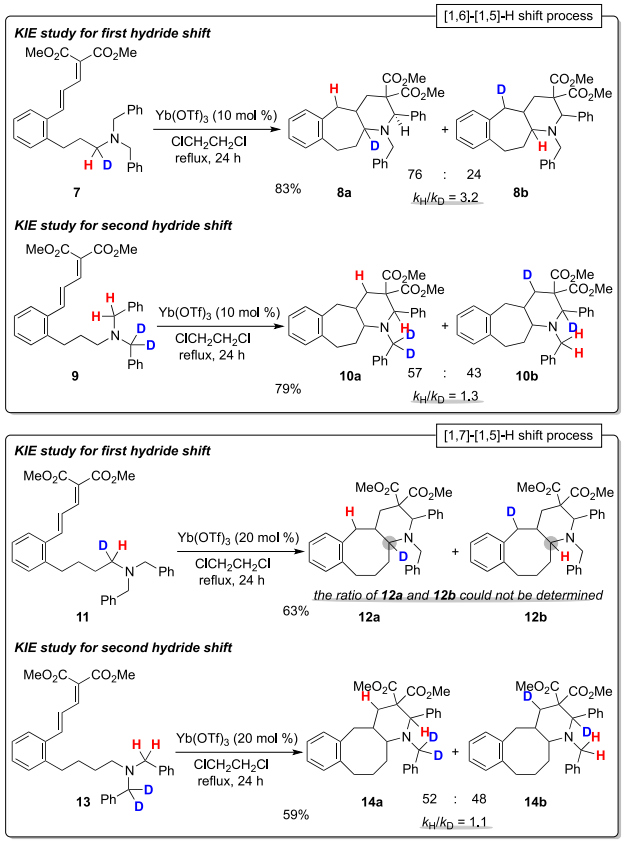


Figure 2. Substrate scope for [1,7]-[1,5]-hydride shift process.

there are several synthetic methods for the formation of eight-membered hetero- and carbo-cycles,[3] the one-pot construction of an 8/6-fused cycle is a quite rare and challenging task. We were pleased to find that the present sequential reaction yielded the target skeleton under slightly modified optimized reaction conditions (increasing the catalyst loading to 20 mol %). When cinnamylidene malonate **5a** with an *N*,*N*-dibenzyl butylamine moiety at the *ortho* position was treated with 20 mol % of $Yb(OTf)_3$ in refluxing $ClCH_2CH_2Cl$, the desired [1,7]-[1,5]-hydride sequence proceeded to give the eight-membered-ring-fused piperidine derivative **6a** in good chemical yield with high diastereoselectivity (78%, d.r. = >20:3.3:2.6:1). As in the case of the [1,6]-[1,5]-hydride shift process, the substituents on the aromatic ring had a negligible effect on this reaction, affording various 8/6-fused cycles **6a**–**f** in good chemical yield with high diastereoselectivities (61–78%, d.r. = up to >20:3.3:2.6:1). X-ray crystallographic analysis of **6a** revealed that the relative stereochemistry of the major diastereomer was identical in both reactions (vide supra).

Deuterium labeling experiments provided important information to help us understand the mechanisms of two sequential reactions (Scheme 3). At first, the involvement of

Scheme 3. KIE Studies for [1,6]-[1,5]-Hydride Shift and [1,7]-[1,5]-Hydride Shift



the primary kinetic isotope effect (KIE) was examined for the [1,6]-[1,5]-hydride shift process (Scheme 3, upper part). A comparison of the k_H/k_D values of the first and second hydride shifts (3.2 for the first hydride shift vs 1.3 for the second hydride shift) suggested that the first hydride shift was the rate-determining step and the second hydride shift was a more facile process than the first one. In regards to the [1,7]-[1,5]-hydride shift process (Scheme 3, lower part), the k_H/k_D value of the first hydride shift could not be determined due to the complicated ^1H NMR spectrum. (The assignment of the peak of key methine proton adjacent to the nitrogen atom, highlighted in gray, was extremely difficult.) Judging from the information enumerated later, we believe that the first hydride shift would also be the rate-determining step in the [1,7]-[1,5]-hydride shift process: (1) The [1,7]-hydride shift

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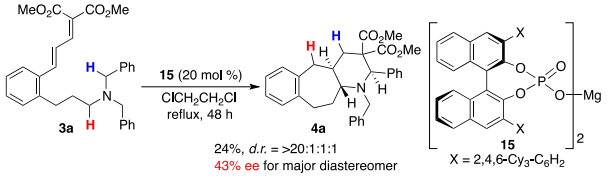
via the labile eight-membered-ring transition state would be more difficult than the [1,6]-hydride shift. This assumption is supported by the fact that an increased catalyst loading (20 vs 5−10 mol %) was required in the former reaction. (2) The first [1,6]-hydride shift was a more difficult process than the second [1,5]-hydride shift in the [1,6]-[1,5]-hydride shift process (vide supra). (3) KIE was not observed in the second hydride shift process in the [1,7]-[1,5]-hydride shift process (k_H/k_D = 1.1).

Motivated by our recent results on the asymmetric double C(sp^3)−H bond functionalization,[11a] an asymmetric variant of the present reaction was examined (Scheme 4). In this case,

Scheme 4. Asymmetric Reaction with Chiral Magnesium Bisphosphate 15



chiral magnesium bisphosphate **15**[16] was the catalyst of choice, and moderate but promising enantioselectivity (43% ee) was achieved.[17] Although the chemical yield is low in this stage (24%), this moderate enantioselectivity clearly indicates the high synthetic potential of the present method for the preparation of medium-sized ring-fused complex organic molecules.

In summary, we developed an effective synthetic method for synthetically challenging, medium-sized carbocycle-fused piperidines via the [1,*n* (*n* = 6, 7)]-[1,5]-sequential hydride shift triggered double C(sp^3)−H bond functionalization. This reaction has two features: (1) the accomplishment of the sequential hydride shifts involving quite rare [1,6]- and [1,7]-hydride shifts and (2) the high stereocontrol of the three newly formed stereogenic centers in the complex fused piperidines. The application of this sequential hydride shift/cyclization strategy to two medium-sized ring-fused compounds is under way.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03498.

Experimental procedures and analytical and spectroscopic data for new compounds (PDF)

Copies of NMR spectra (PDF)

Accession Codes

CCDC 1952790−1952792 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: k_mori@cc.tuat.ac.jp.

ORCID

Keiji Mori: 0000-0002-9878-993X

Notes

The authors declare no competing financial interest.

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