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Organocatalytic Reduction of Carbon−Carbon Double Bonds in Racemization-Sensitive Compounds

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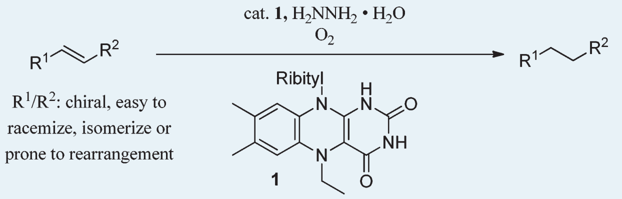
S *Supporting Information*

ABSTRACT: *N*-ethyl riboflavin efficiently catalyzes the hydrazine mediated reduction of carbon−carbon double bonds. This strategy allows chemo-selective reductions in complex molecules that are prone to racemization, olefin isomerization, or hydrogenolysis in transition metal-catalyzed hydrogenations. The high functional group tolerance of this methodology is demonstrated as well.



KEYWORDS: reduction, organocatalysis, diimide, alkenes, flavins

INTRODUCTION

Inspired by nature's use of flavin cofactors such as riboflavin, and flavin adenine mono- and dinucleotide (FMN, FAD) in redox-active enzymes, for example, monooxygenases,[1−4] flavin derivatives have recently been introduced as organocatalysts in organic synthesis.[5−21] The various applications include catalytic sulfoxidation of thioethers,[6,7,9,12] oxidation of amines to the corresponding *N*-oxides,[10] Baeyer−Villiger oxidation of ketones,[13,14,22] reduction of alkenes[15,21,23] as well as the use of flavin derivatives as cocatalysts in Os-catalyzed dihydroxylation of alkenes.[16−18,24,25] Riboflavin-based organocatalysts offer a green and low-cost alternative to the corresponding metal-catalyzed transformations, also because dioxygen or hydrogen peroxide are used as the terminal oxidants.

On the basis of an initial report of Imada and co-workers,[15] we recently disclosed our results on the efficient reduction of carbon−carbon double bonds employing a riboflavin-based organocatalyst and hydrazine in air.[21] Therein, *N*-ethyl-riboflavin **1**, prepared in one step from readily available riboflavin (vitamin B_2), acts as a catalyst for the formation of diimide (diazene, HN=NH) from hydrazine, which is the actual reductant (Scheme 1). The facts that low cost hydrazine hydrate is used and that the production of diimide is much better controlled compared to the classical oxidation methods, make this an extremely versatile method. Very recently, the group of Imada further extended the potential of flavin catalysts with the development of a two-phase system allowing the recycling of their catalysts.[23]

In general, reduction of olefins is carried out using transition metals, in either a hetero- or a homogeneous fashion.[26] However, the application of these methods is problematic when one considers structurally sophisticated molecules, such as shown in Figure 1. Here, transition metal-catalyzed reduction of the double bonds indicated leads to side-reactions or complete failure. The double bond in ester **2** is prone to isomerization to the more stable triple substituted alkene, which upon reduction erodes the e.e. of the product. Although racemization could possibly be minimized by careful selection of the transition metal-catalyst, it is virtually impossible to determine the e.e. of the hydrogenation product a posteriori, so this selection is severely hampered. Olefins **3** to **6** carry a chiral center adjacent to the double bond. These and related structures often show isomerization of the double bond to the in-conjugation position and thus racemize upon hydrogenation.[27−37] In addition, **4** is prone to hydrogenolysis in particular when applying heterogeneous Pd catalysts, whereas heterogeneous Pt and Rh catalysts hydrogenate the naphthyl functions. Vinylcyclopropanes such as **7** are prone to rearrange with a variety of transition metal complexes as catalysts[38,39] and hence represent another class of olefins that are extremely difficult to reduce under both homogeneous and heterogeneous hydrogenation conditions. In a recent study by Burgess et al., it was shown that the acidity of the catalytic intermediates in homogeneous olefin hydrogenation plays a major role with regard to olefin isomerization.[42] Finally, undesired hydrogenolysis of additional functional groups such as benzylic and propargylic alcohols and amines impose synthetic problems.[40,41]

Diimide reduction of double bonds follows a concerted mechanism and is selective for nonpolarized carbon−carbon bonds. Moreover, the mechanism of the reaction precludes any isomerization (racemization) and hydrogenolysis which makes this method ideal for application in complex systems.[43]

Herein, we present the application of flavin-based catalyst **1** for the reduction of these functionalized substrates. In part, the compounds are intermediates of synthetic routes to complex (natural) products, and in part we developed routes to especially sensitive compounds to challenge this flavin/hydrazine reduction system. A procedure for the reduction of sterically hindered substrates is disclosed as well.

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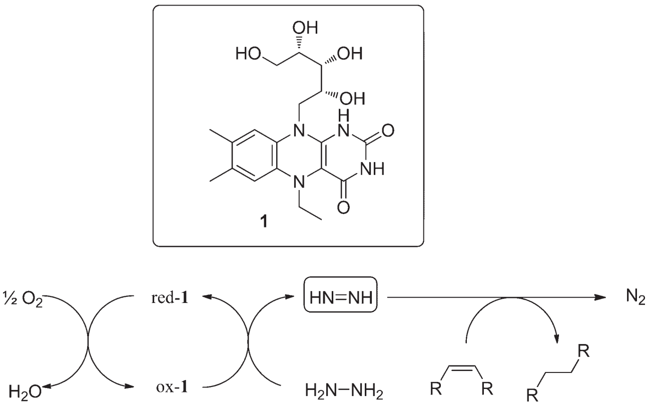
Scheme 1. Riboflavin Catalyst 1 and Its Proposed Catalytic Cycle



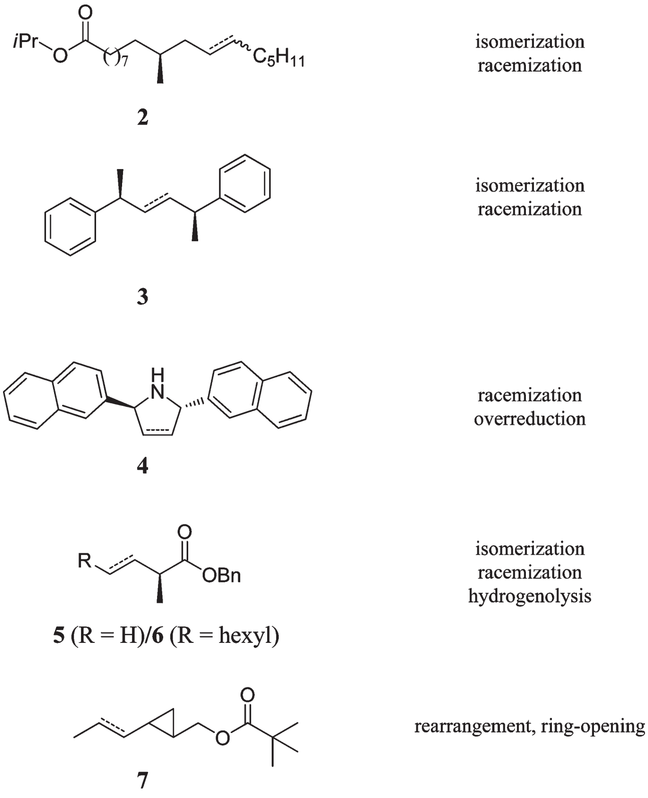


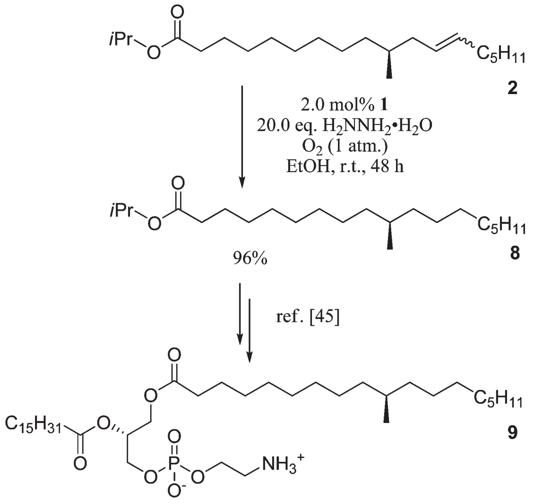
Figure 1. Examples of olefins and their problems in homogeneous or heterogeneous hydrogenation.

■ RESULTS AND DISCUSSION

The combination of olefination reactions or cross-metathesis methodology[44] with the organocatalytic reduction of double bonds is an efficient pathway for the construction of aliphatic chains. These are frequently occurring in natural products, and enable molecules to anchor to, or penetrate in, the cellular membranes. From a synthetic point of view, it is desirable to functionalize a molecule *before* aliphatic chains are attached, since the latter often leads to solubility problems in polar organic solvents.

En route to the total synthesis of glycerophospholipid **9** found in *Mycobacterium tuberculosis*,[45] ester **2** was synthesized with 90% e.e. via asymmetric Cu-catalyzed conjugate addition to the unsaturated thioester[46−48] followed by reduction to the corresponding aldehyde and subsequent Wittig olefination. **2** was then reduced to isopropyl ester **8** by the riboflavin-catalyzed formation of diimide. With 2.0 mol % of catalyst **1** and an excess of hydrazine, the desired product was isolated in 96% yield (Scheme 2).

Scheme 2. Organocatalytic Reduction of an Internal Olefin in the Synthesis of Glycerophospholipid 9



An elegant example of the application of our organocatalytic reduction methodology is displayed in the synthesis of compound **12**, carrying two stereocenters in a 1,4-relationship (Scheme 3). Here, cross metathesis in combination with reduction is also employed successfully. The stereocenters are introduced in excellent yield and enantioselectivity (87%, and 99%, respectively) by asymmetric Cu-catalyzed allylic alkylation with methylmagnesium bromide employing ferrocenyl ligand **L1**.[49,50] The resulting terminal alkene **11** was subsequently dimerized to olefin **3** by cross metathesis. Attempts to hydrogenate the double bond with palladium-catalysts would invariably lead to partial isomerization. Reduction of **3** employing 20 mol % of riboflavin **1** and an excess of hydrazine (see Scheme 1), added in 3 portions over time, gave the desired product in excellent yield (96%), without detectable racemization (d.e. > 98%). Alternatively, **12** has been prepared in high e.e. via iridium-catalyzed asymmetric hydrogenation of 2,5-diphenyl-1,5-hexadiene.[51]

Substituted pyrrolidines represent asymmetric organocatalysts[52−59] as well as key structural features of chiral phosphoramidite ligands.[60,61] In this context we investigated the reduction of sterically hindered enantiopure (99% e.e.) pyrroline **4** to pyrrolidine **13** (Table 1).[62] The reduction was initially attempted using dihydrogen and a homogeneous Rh-complex; however, no turnover was found. Furthermore, the attempted reduction of the double bond with *o*-nitrobenzenesulfonylhydrazide[63−65] led to no conversion. On the contrary, catalytic amounts of riboflavin **1** led to some conversion of pyrroline **4** (Table 1, entry 1). When 50 mol % of the organocatalyst **1** with respect to pyrroline **4** was employed, only 50% conversion was reached (entry 2). However, employing a slow addition protocol of solutions of both catalyst and hydrazine over a period of 10 h, the same amount of **1** gave rise to 80% conversion (Table 1, entry 3). Finally, when stoichiometric amounts of **1** with respect to **4** were employed under these optimized conditions (entry 4), full conversion was

Scheme 3. Organocatalytic Reduction in the Synthesis of 12

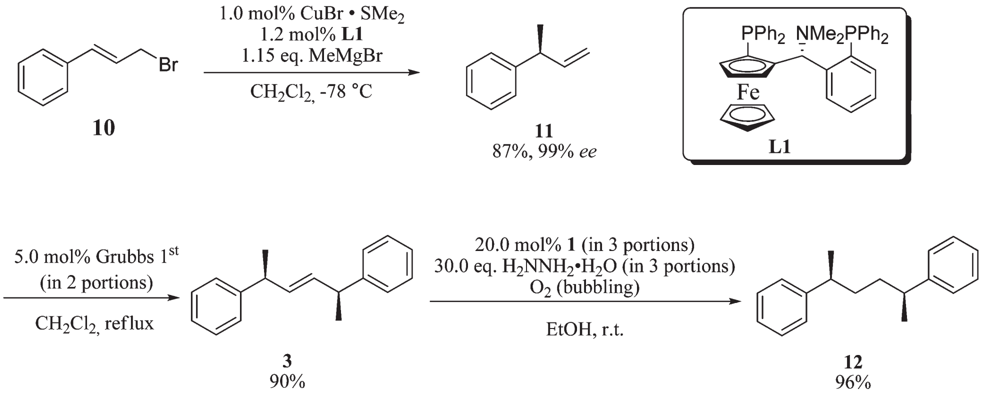
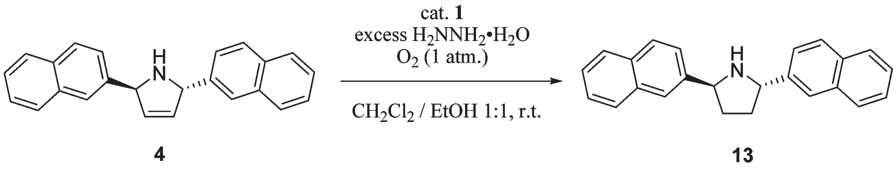


Table 1. Optimization of Reduction of Pyrroline 4



entry	cat. loading of **1** (mol %)	conversion
1	10	traces
2	50[a]	50%
3	50[b]	80%
4	100[b]	full[c]

[a] **1** and hydrazine hydrate added in 5 min. [b] **1** and hydrazine hydrate added slowly over a period of 10 h. [c] 81% isolated yield.

reached and the product was isolated in good yield (81%). It is important to note that even though **1** is used in a stoichiometric amount with respect to the substrate **4**, it can still be referred to as a catalyst since it catalyzes the formation of diimide from hydrazine, to which it is still present in catalytic amounts. No racemization was observed as the other diastereomer was not detected by ^{1}H NMR, and no protection of the secondary amine was necessary, making this organocatalytic reduction protocol ideal for the synthesis of the desired chiral pyrrolidine **13**.

The success of the slow-addition protocol for sterically demanding substrates can be explained by the fact that the catalyst as well as the diimide have a limited lifetime under the employed reaction conditions. The active concentration of reducing agent is effectively lowered during the reaction by diimide disproportionation to dinitrogen and hydrazine.[66,67] By adding the organocatalyst and hydrazine slowly to the mixture, the active concentration of diimide stays constant during the reaction, allowing for higher turnover in the reduction of sterically demanding substrates.

These optimized reactions conditions were also required for the reduction of β,γ-unsaturated α-chiral esters **5** (98% e.e.) and **6** (98% e.e.), which are important chiral building blocks for organic synthesis (Tables 2, 3).[68] Here, reduction of the double bond was investigated initially with Pd/C and hydrogen, but led to a significant amount of isomerization of the double bond of **5** into the conjugated position, as determined by ^{1}H NMR. For example, with 0.25% Pd (using 5 wt % of Pd/C) full conversion of **5** was reached in 1 h (Table 2, entry 1), but substantial isomerization of the double bond was observed. Lowering the amount of the catalyst to 0.10% Pd led to a significant decrease of conversion (entry 2). With 5 mol % of riboflavin **1** and an excess of hydrazine, full conversion was reached; however, the formation of benzylalcohol was observed, possibly because of hydrazide formation (entry 3). To prevent the latter side reaction, the amount of hydrazine was lowered, which in turn led to lower conversion, even when more riboflavin **1** was employed (entries 4 and 5). When only the hydrazine was added slowly, even lower conversion was observed, indicating a limited lifetime of **1** (entry 6) under the given reaction conditions. When the optimized slow addition protocol (entries 3−4) was employed, however, full conversion along with a minimum amount of isomerization was found, and the product could be isolated in 91% yield without loss of stereochemical integrity as shown by chiral GC (entry 7).

The reduction of chiral benzyl esters such as **6** bearing an internal olefin proved to be viable with **1** also (Table 3, entries 1−4). Just as in the previous case (Table 1), steric hindrance played a significant role, and to reach acceptable conversions, much higher catalyst loadings were necessary. With the slow addition of 100 mol % of organocatalyst **1** with respect to substrate **6** (1.8 mol % with respect to hydrazine), a maximum of 89% conversion was reached which afforded a somewhat lower isolated yield (75%) (Table 3, entry 4).

The reduction of an alkene adjacent to a cyclopropane is notoriously difficult because the use of transition metals leads almost invariably to ring-opening. Nevertheless, as cyclopropane

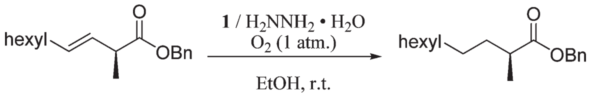
Table 2. Reduction of Unsaturated Ester 5

5 14

entry	method	hydrazine (eq)	reduction	isomerization
1	Pd/C[a]		full	24%
2	Pd/C[b]		40%	9%
3	5 mol % **1**[c]	20	full[d]	<5%
4	5 mol % **1**[c]	7.5	~90%	<5%
5	20 mol % **1**[c]	7.5	81%	3%
6	20 mol % **1**[c]	7.5	48%[e]	5%
7	20 mol % **1**[c]	10	full[f,g]	<5%

[a] 0.25% Pd based on 5 wt % Pd/C, H_2 (1 atm), EtOAc, rt [b] 0.10% Pd based on 5 wt % Pd/C, H_2 (1 atm), EtOAc, rt [c] O_2 (1 atm), EtOH, rt [d] Formation of benzylalcohol observed. [e] Hydrazine was added slowly. [f] **1** and hydrazine hydrate added slowly over a period of 1 h. [g] Isolated yield of **14**: 91%, >95% e.e.

Table 3. Reduction of Unsaturated Ester 6



6 15

entry	cat **1** (mol %)	hydrazine (eq)	reduction	isomerization
1	50	15	65%[a]	<5%
2	50	30	76%[a]	<5%
3	100	40	81%[a]	<5%
4	100	54	89%[a,b]	<5%

[a] **1** and hydrazine hydrate added slowly over a period of 6 h. [b] Isolated yield of **15**: 75%.

units are often incorporated in a molecule via a combination of building blocks and an olefination reaction, it is a regularly encountered task. Diimide reductions are mostly used, as is, for example, shown nicely in the synthesis of mycolic acids by Baird et al.[69,70] However, yields tend to vary substantially depending on the substrate and the way in which the diimide is generated.

To obtain a model substrate, we prepared **7** by Simmons—Smith reaction of dienol **16** which gave a mixture of alcohols **17** in which either one or two of the olefins had reacted to the desired cyclopropane. After esterification with pivalic acid, the undesired compound could be separated from **7**. Vinylcyclopropane **7** was successfully converted to the corresponding saturated cyclopropane by using the optimized conditions (Scheme 4). The product was obtained in excellent yield (84%) without any side-reaction observed. This represents an important feature of our reduction protocol, since vinylcyclopropanes are extremely difficult to reduce with transition-metal based methods without compromising the cyclopropane moiety.

CONCLUSIONS

In conclusion, it is shown that organocatalytic generation of diimide using ethyl-flavin **1** dramatically improves the efficiency of diimide in carbon—carbon double bond reduction reactions. This makes the riboflavin/hydrazine system a valuable alternative for transition metal-catalyzed hydrogenation reactions in particular for more complex substrates. As shown explicitly in a variety of cases, effective double bond reduction using diimide is often a *conditio sine qua non* for success of a synthetic strategy. The new reaction protocol, allows the transformation of sterically demanding substrates and leads to a higher turnover. In addition to avoiding metal-catalyzed hydrogenation with its tendency for double bond isomerization and hydrogenolysis, the current method is highly chemo-selective. Finally, this reaction might find application in cases where metal contamination of the product is prohibited such as in the preparation of pharmaceuticals and in nanotechnology.

EXPERIMENTAL SECTION

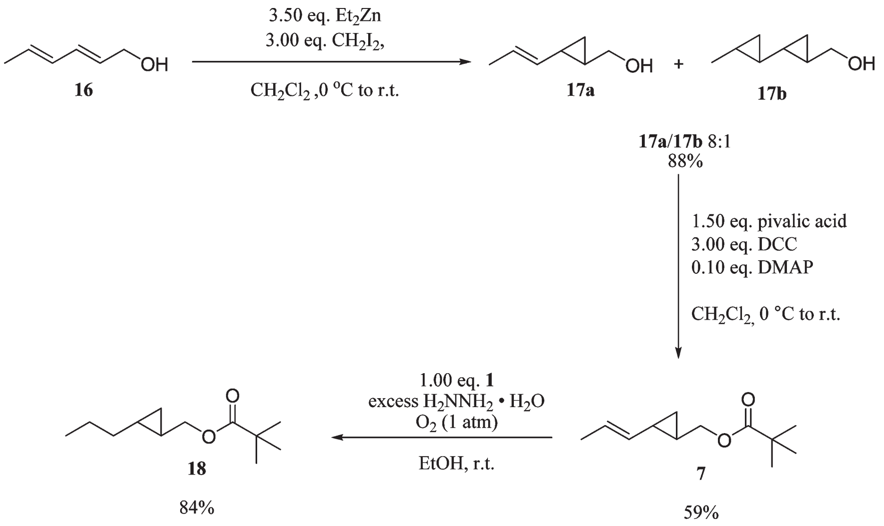
Riboflavin catalyst **1** was prepared according to a previously described procedure.[21]

General Procedure for the Reduction of Double Bonds with 1/Hydrazine. ***Caution!*** *Hydrazine is a suspected cancer agent.* The appropriate olefin (0.50 mmol, 1.0 equiv) was dissolved in 10 mL of EtOH at room temperature (rt) and stirred vigorously. An atmosphere of oxygen was applied (balloon, 1 atm). Then, via a syringe pump, a solution of riboflavin catalyst **1** (0.05 mmol, 0.1 equiv) in EtOH (5 mL) was added slowly via syringe and, via a second syringe, hydrazine hydrate (5.0 mmol, 10 equiv) was added over a period of 10 h. The reaction mixture was stirred at rt for another 6 h and progress of the reaction was followed by ^1H NMR (samples were washed with water and extracted with CH_2Cl_2). CH_2Cl_2 was added (20 mL), and subsequently, the mixture was washed with water (3 × 10 mL), the aqueous layers were reextracted with CH_2Cl_2 (10 mL), and the organic layers combined. After drying (Na_2SO_4), volatiles were removed in vacuo to yield the crude product. This was purified by column chromatography (SiO_2).

*(S)-But-3-en-2-ylbenzene (**11**)*[50]. In a Schlenk tube equipped with septum and stirring bar, CuBr·SMe_2 (1 mol %, 0.156 g, 0.76 mmol), and (+)-taniaphos (1.2 mol %, 0.631 g, 0.916 mmol) were dissolved in 115 mL of dry CH_2Cl_2 and stirred under N_2 for 10 min at rt. The mixture was then cooled to −78 °C and MeMgBr (1.10 equiv, 29.3 mL, 87.8 mmol) was added dropwise. Cinnamyl bromide (1.0 equiv, 15.0 g, 76.1 mmol) was then added as a solution in 35 mL of CH_2Cl_2 over 1 h via syringe pump. The reaction was followed by TLC and stopped after 15 h by adding 25 mL of MeOH at −78 °C. After 10 min at −78 °C the mixture was allowed to warm to rt. Aqueous NH_4Cl solution (1 M, 100 mL) was added, and the organic phase was separated. The resulting aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and partially concentrated under reduced pressure. The product was purified by distillation under reduced pressure to yield 8.79 g (87%) of **11** as a colorless liquid. The *ee* was determined by GC on a CP-Chiralsil-Dex-CB (25 m × 0.25 mm) column. T = 75 °C, retention times: minor: 17.75 min, major: 18.07 min, *ee* = 99.5%. $[\alpha]_D$ +5.4 (c 1.2, $CHCl_3$). The NMR data were in accordance with literature.[50]

*(2S,5S,E)-Hex-3-ene-2,5-diyldibenzene (**3**)*[71]. A dried 250 mL flask was charged with **11** (1.0 equiv, 8.00 g, 60.5 mmol) and 60 mL of CH_2Cl_2, and subsequently nitrogen was passed through the solution for 30 min. Grubbs first generation catalyst (5.0 mol %, 3.00 mmol, 2.50 g) was then added, and the resulting solution was stirred at reflux. After 48 h, 2.50 mol % of Grubbs first generation catalyst was added, and the reaction was stirred at

Scheme 4. Organocatalytic Reduction of Vinylcyclopropane 7



reflux for an additional 48 h. The reaction was stopped by removing the solvent under reduced pressure. The crude mixture was purified by flash chromatography (pentane) to yield 6.39 g (90%) of **3** as a colorless oil. $[\alpha]_D$ +11.5 (*c* 0.80, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33−7.29 (m, 4H), 7.24−7.18 (m, 6H), 5.68 (dd, *J* = 3.6, 1.6 Hz, 2H), 3.47 (m, 2H), 1.37 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.3 (C), 133.7 (CH), 128.3 (CH), 127.2 (CH), 125.9 (CH), 42.1 (CH), 21.5 (CH$_3$) ppm.

*(2S,5S)-Hexane-2,5-diyldibenzene (**12**)*[50]. In a 3-necked round-bottom flask, **3** (4.20 g, 17.8 mmol) was dissolved in 75 mL of ethanol. Oxygen was passed through the solution continuously. A solution of **1** (10 mol %, 1.78 mmol, 0.711 g) in 15 mL of ethanol was then added. Finally, hydrazine hydrate (30 equiv, 534 mmol, 27 mL) was added, and the reaction was stirred vigorously. After 6 h, an additional 5.0 mol % of **1** and 5.0 mL of hydrazine hydrate were added. Again, after 24 h, 5.0 mol % of **1** and 5.0 mL of hydrazine hydrate were added. The reaction was followed by TLC and stopped after 55 h. The crude mixture was concentrated to 50 mL and then diluted with 100 mL of water. The solution was extracted 4 times with pentane, and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated to yield 4.06 g (96%) of **12** as a colorless oil. $[\alpha]_D$ +23.0 (*c* 1.05, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34−7.12 (m, 10H), 2.69−2.62 (m, 2H), 1.56−1.46 (m, 4H), 1.21 (d, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.6 (C), 128.2 (CH), 127.0 (CH), 125.8 (CH), 40.0 (CH), 36.1 (CH$_2$), 22.6 (CH$_3$) ppm. The compound has been reported before, see ref 50.

*(E)-(2-(Prop-1-en-1-yl)cyclopropyl)methanol (**17**).* A solution of diethylzinc (25.5 mL, 25.5 mmol, 2.5 equiv, 1 M in hexane) in CH$_2$Cl$_2$ (40 mL) was cooled to 0 °C. Diiodomethane (2.5 mL, 30.6 mmol, 3.0 equiv) was added dropwise. The resulting mixture was stirred at the same temperature for 15 min before 2,4-hexadien-1-ol **16** (1.2 mL, 10.2 mmol, 1 equiv) was added dropwise. The reaction mixture was allowed to warm up to rt. The progress of the reaction was followed by GC-MS. After 30 h, diethylzinc (10 mL, 10 mmol) was added at 0 °C to ensure full conversion. The mixture was allowed to reach rt and was stirred for another 4 h. GC-MS analysis showed no further conversion; therefore diiodomethane (2 mL, 24.8 mmol, 2.40 equiv) was added at rt. The reaction mixture was quenched by addition of saturated aq. NH$_4$Cl solution after stirring at rt for additional 38 h. The phases were separated, and the aqueous layer was extracted three times with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$, and all volatiles were removed under reduced pressure. The crude product was purified by column chromatography (SiO$_2$, pentane/diethyl ether 10:1 to 4:1) to yield a mixture of **17a** and **17b** (1.00 g, 88% **17a**/**17b**: 8:1) as a yellow oil. *Rf* = 0.36 (pentane/diethyl ether, 1:1) Major component: (**17a**): ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.01 (s, 1H), 5.55−5.46 (m, 1H), 5.08−5.02 (ddt, *J* = 15.2, 8.3, 1.6 Hz, 1H), 3.51−3.38 (m, 2H), 1.65−1.63 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.10−1.05 (m, 1H), 0.75−0.67 (m, 1H), 0.62−0.55 (m, 1H), 0.53−0.42 (m, 1H), 0.34−0.26 (m, 1H), 0.22−0.17 (m, 1H), 0.11−0.05 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 132.9 (CH), 123.4 (CH), 66.6 (CH$_2$), 22.5 (CH), 19.4 (CH$_3$), 11.2 (CH$_2$). HRMS-ESI$^+$: m/z $[M + H]^+$ calcd for C$_7$H$_{13}$O: 113.0966; found: 113.0961.

*(E)-(2-(Prop-1-en-1-yl)cyclopropyl)methyl pivalate (**7**).* Pivalic acid (1.37 g, 13.4 mmol, 1.5 equiv) was dissolved in 15 mL of CH$_2$Cl$_2$ and cooled to 0 °C. To this solution were added DCC (5.55 g, 26.9 mmol, 3.0 equiv) and DMAP (109 mg, 0.89 mmol, 0.1 equiv), and the reaction mixture was stirred for 5 min at 0 °C before a solution of alcohols **17a** and **17b** (1.00 g, 8.96 mmol, 1.0 equiv) in 5 mL of CH$_2$Cl$_2$ was added. The reaction mixture was allowed to warm up to rt and was stirred at that temperature for 24 h. The reaction was worked up by filtration over Celite and washing with pentane. The crude product was purified by column chromatography (SiO$_2$, pentane/MTBE 10:1 to 2:1) to yield ester **7** as a yellow oil. (1.03 g, 5.25 mmol, 59%). *Rf* = 0.77 (pentane/MTBE, 1:1) ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.50−5.43 (m, 1H), 5.04−5.02 (ddt, *J* = 15.1, 8.1 Hz, 1H), 3.93−3.84 (m, 2H), 1.58 (d, *J* = 6.4 Hz, 3H), 1.15 (s, 9H), 1.05 (m, 1H), 0.72 (m, 1H), 0.61−0.57 (m, 1H), 0.55−0.52 (m, 1H), 0.42 (m, 1H), 0.23 (m, 1H), 0.13 (m, 1H), 0.02 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 178.5 (C), 132.7 (CH), 123.6 (CH), 67.6 (CH$_2$), 34.2 (C), 27.1 (3 × CH$_3$), 19.4 (CH$_3$), 18.7 (CH), 17.6 (CH), 11.4 (CH$_2$).

*(2-Propylcyclopropyl)methyl pivalate (**18**).* **7** (100 mg, 0.51 mmol, 1.0 equiv) was converted to **18** following the general procedure for the reduction of double bonds with **1**/hydrazine.

The crude product was purified by column chromatography (SiO$_2$, pentane/diethyl ether 50:1 to 9:1) to yield ester **18** as yellow oil (85 mg, 0.43 mmol, 84%). *Rf* = 0.69 (pentane/diethyl ether, 4:1) ^{1}H NMR (500.0 MHz CDCl$_3$): δ 8.01 (s, 1H), 5.55−5.46 (m, 1H), 5.08−5.02 (ddt, *J* = 15.2, 8.3, 1.6 1H), 3.51−3.38 (m, 2H), 1.65−1.63 (dd, *J* = 6.5, 1.6, 3H), 1.10−1.05 (m, 1H), 0.75−0.67 (m, 1H), 0.62−0.55 (m, 1H), 0.53−0.42 (m, 1H), 0.34−0.26 (m, 1H), 0.22−0.17 (m, 1H), 0.11−0.05 (m, 1H). ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 178.7 (C), 68.5 (CH$_2$), 38.7 (C), 27.2 (CH$_2$), 27.1 (3 × CH$_3$), 22.5 (CH$_2$), 17.2 (CH), 13.9 (CH$_3$), 10.0 (CH$_2$). HRMS-ESI$^+$: m/z [M + Na]$^+$ calcd for C$_7$H$_{12}$O: 221.1517; found: 221.1512.

ASSOCIATED CONTENT

S **Supporting Information.** General experimental information and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Schlaich, N. L. *Trends Plant Sci.* **2007**, *12*, 412–418.

(2) van Berkel, W. J. H.; Kamerbeek, N. M.; Fraaije, M. W. *J. Biotechnol.* **2006**, *124*, 670–689.

(3) van Hellemond, E. W.; Leferink, N. G. H.; Heuts, D.; Fraaije, M. W.; van Berkel, W. J. H. *Adv. Appl. Microbiol.* **2006**, *60*, 17–54.

(4) De Colibus, L.; Mattevi, A. *Curr. Opin. Struct. Biol.* **2006**, *16*, 722–728.

(5) Baxová, L.; Cibulka, R.; Hampl, F. *J. Mol. Catal. A: Chem.* **2007**, *277*, 53–60.

(6) Imada, Y.; Iida, H.; Ono, S.; Masui, Y.; Murahashi, S. I. *Chem. Asian. J.* **2006**, *1*, 136–147.

(7) Lindén, A. A.; Johansson, M.; Hermanns, N.; Bäckvall, J. E. *J. Org. Chem.* **2006**, *71*, 3849–3853.

(8) Lindén, A. A.; Kruger, L.; Bäckvall, J. E. *J. Org. Chem.* **2003**, *68*, 5890–5896.

(9) Imada, Y.; Iida, H.; Ono, S.; Murahashi, S. I. *J. Am. Chem. Soc.* **2003**, *125*, 2868–2869.

(10) Minidis, A. B. E.; Bäckvall, J. E. *Chem.—Eur. J.* **2001**, *7*, 297–302.

(11) Bergstad, K.; Bäckvall, J. E. *J. Org. Chem.* **1998**, *63*, 6650–6655.

(12) Murahashi, S. I.; Oda, T.; Masui, Y. *J. Am. Chem. Soc.* **1989**, *111*, 5002–5003.

(13) Imada, Y.; Iida, H.; Murahashi, S.; Naota, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1704–1706.

(14) Mazzini, C.; Lebreton, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 8–9.

(15) Imada, Y.; Iida, H.; Naota, T. *J. Am. Chem. Soc.* **2005**, *127*, 14544–14545.

(16) Bergstad, K.; Jonsson, S. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 10424–10425.

(17) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 357.

(18) Sundermeyer, U.; Dábler, C.; Beller, M. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004; p 1.

(19) Murahashi, S. I.; Ono, S.; Imada, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 2366–2368.

(20) Shinkai, S.; Yamaguchi, T.; Manabe, O.; Toda, F. *J. Chem. Soc., Chem. Commun.* **1988**, 1399–1401.

(21) Smit, C.; Fraaije, M. W.; Minnaard, A. J. *J. Org. Chem.* **2008**, *73*, 9482–9485.

(22) Kamerbeek, N. M.; Janssen, D. B.; van Berkel, W. J. H.; Fraaije, M. W. *Adv. Synth. Catal.* **2003**, *345*, 667–678.

(23) Imada, Y.; Kitagawa, T.; Ohno, T.; Iida, H.; Naota, T. *Org. Lett.* **2010**, *12*, 32–35.

(24) Jonsson, S. Y.; Adolfsson, H.; Bäckvall, J. E. *Org. Lett.* **2001**, *3*, 3463–3466.

(25) Jonsson, S. Y.; Färnegårdh, K.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 1365–1371.

(26) *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2006.

(27) Parvulescu, A.; De Vos, D.; Jacobs, P. *Chem. Commun.* **2005**, 5307–5309.

(28) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem.—Eur. J.* **2007**, *13*, 2034–2043.

(29) Yajima, A.; Qin, Y.; Zhou, X.; Kawanishi, N.; Xiao, X.; Wang, J.; Zhang, D.; Wu, Y.; Nukada, T.; Yabuta, G.; Qi, J. H.; Asano, T.; Sakagami, Y. *Nat. Chem. Biol.* **2008**, *4*, 235–237.

(30) Nishimura, T.; Guo, X. X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576.

(31) Nakai, T.; Yajima, A.; Akasaka, K.; Kaihoku, T.; Ohtaki, M.; Nukada, T.; Ohrui, H.; Yabuta, G. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 2401–2408.

(32) Dandapani, S.; Jeske, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 9447–9462.

(33) Schwartz, B. D.; Hayes, P. Y.; Kitching, W.; De Voss, J. J. *J. Org. Chem.* **2005**, *70*, 3054–3065.

(34) Mori, K.; Ohtaki, T.; Ohrui, H.; Berkebile, D. R.; Carlson, D. A. *Eur. J. Org. Chem.* **2004**, 1089–1096.

(35) Smith, G. V.; Wang, Y.; Song, R.; Jackson, M. *Catal. Today* **1998**, *44*, 119–127.

(36) Rakoff, H.; Rohwedder, W. K. *Lipids* **1992**, *27*, 567–569.

(37) Smith, G. V.; Roth, J. A.; Desai, D. S.; Kosco, J. L. *J. Catal.* **1973**, *30*, 79–85.

(38) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179.

(39) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229–267.

(40) Galletti, A. M. R.; Bonaccorsi, F.; Calvani, F.; Di Bugno, C. *Catal. Commun.* **2006**, *7*, 896–900.

(41) Wilkinson, H. S.; Hett, R.; Tanoury, G. J.; Senanayake, C. H.; Wald, S. A. *Org. Process Res. Dev.* **2000**, *4*, 567–570.

(42) Zhu, Y.; Fan, Y. B.; Burgess, K. *J. Am. Chem. Soc.* **2010**, *132*, 6249–6253.

(43) Pasto, D. J.; Taylor, R. T. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40, p 91.

(44) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765.

(45) ter Horst, B.; Seshadri, C.; Sweet, L.; Young, D. C.; Feringa, B. L.; Moody, D. B.; Minnaard, A. J. *J. Lipid. Res.* **2010**, 1017.

(46) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–188.

(47) Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966–9967.

(48) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039–1075.

(49) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.

(50) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409–411.

(51) Cui, X. H.; Ogle, J. W.; Burgess, K. *Chem. Commun.* **2005**, 672–674.

(52) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560.

(53) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821–4823.

(54) Chen, H. F.; Sweet, J. A.; Lam, K. C.; Rheingold, A. L.; McGrath, D. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1672–1682.

(55) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791.

(56) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507–5510.

(57) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151–4157.

(58) Shi, M.; Satoh, Y.; Masaki, Y. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 2547–2552.

(59) Sweet, J. A.; Cavallari, J. M.; Price, W. A.; Ziller, J. W.; McGrath, D. V. *Tetrahedron: Asymmetry* **1997**, *8*, 207–211.

(60) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 12398–12399.

(61) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486–2528.

(62) Teichert, J. F.; Feringa, B. L. *Synthesis* **2010**, 1200–1204.

(63) Buszek, K. R.; Brown, N. *J. Org. Chem.* **2007**, *72*, 3125–3128.

(64) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507–7507.

(65) Marsh, B. J.; Carbery, D. R. *J. Org. Chem.* **2009**, *74*, 3186–3188.

(66) Tang, H. R.; McKee, M. L.; Stanbury, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 8967–8973.

(67) Pasto, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 6852–6857.

(68) Den Hartog, T.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2010**, *352*, 999–1013.

(69) Koza, G.; Theunissen, C.; Al Dulayymi, J. R.; Baird, M. S. *Tetrahedron* **2009**, *65*, 10214–10229.

(70) Al Dulayymi, J. R.; Baird, M. S.; Roberts, E.; Deysel, M.; Verschoor, J. *Tetrahedron* **2007**, *63*, 2571–2592.

(71) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379.