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Enantioselective Synthesis of Cyclobutanes via Sequential Rh-catalyzed Bicyclobutanation/Cu-catalyzed Homoconjugate Addition

Robert Panish, Srinivasa R. Chintala, David T. Boruta, Yinzhi Fang, Michael T. Taylor, and Joseph M. Fox

Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716

Abstract

Enantiomerically enriched cyclobutanes are constructed by a three-component process in which *t*-butyl (*E*)-2-diazo-5-arylpent-4-enoates are treated with $\text{Rh}_2(\text{S-NTTL})_4$ to provide enantiomerically enriched bicyclobutanes, which can subsequently engage in homoconjugate addition/enolate trapping sequence to give densely functionalized cyclobutanes with high diastereoselectivity. This three-component, two-catalyst procedure can be carried out in a single flask. $\text{Rh}_2(\text{S-NTTL})_4$ -catalyzed reaction of *t*-butyl (*Z*)-2-diazo-5-phenylpent-4-enoate gives the Buchner cyclization product in excellent enantioselectivity.

Stereochemically-rich cyclobutanes are prevalent sub-units in natural products with diverse biological activity.¹ A number of methods have been developed for cyclobutane synthesis,² including photochemical [2+2] cycloadditions,^{1c,d,3,4} catalyzed [2+2] cycloadditions,^{4,5} cyclobutanone syntheses via ketenes,⁶ ring expansion of cyclopropylcarbinyl precursors,⁷ and cyclobutanes CH activation.⁸ Despite advances, there remains a need for new approaches to functionalized cyclobutanes.

Bicyclobutanes are intriguing precursors to functionalized cyclobutanes⁹ which display unusual reactivity as a consequence of their unusual bonding and high strain energy (63.9 kcal/mol).¹⁰ However, the synthetic applications of bicyclobutanes have been relatively limited. In a striking series of papers, Wipf has shown that bicyclobutane derivatives are capable of catalyst promoted ring expansion reactions,^{11a} formal [2+2] cycloadditions,^{11b} and Alderene reactions.^{11c-e} These examples illustrate how complexity can be rapidly generated in strain-releasing reactions of bicyclobutanes.

We envisioned that cyclobutanes could be constructed via bicyclobutane intermediates with the multicomponent process shown in Scheme 1, in which an α -allyl- α -diazocarbonyl compound (**A**) is treated with a chiral catalyst to provide an enantiomerically enriched bicyclobutane (**B**). We envisioned that intermediate **B** could subsequently engage in homoconjugate addition to give enolate (**C**) and subsequent enolate trapping to give densely functionalized cyclobutanes (**D**).

To realize Scheme 1, a challenge was to develop a protocol for homoconjugate addition of organometallic nucleophiles to bicyclobutanecarboxylates. In seminal studies, Gaoni showed that cuprate reagents can add across the central C-C bond of 1-sulfonyl

bicyclobutanes.¹² The diastereoselectivity for such processes was variable. Moreover, analogous reactions of other bicyclobutane derivatives were unknown. While bicyclobutanecarboxylates have been known since 1959,¹³ homoconjugate additions to unsubstituted bicyclobutanecarboxylates had been limited to additions of thiolate and alkoxide nucleophiles.¹⁴

Also critical for the enantioselective bicyclobutanation in Scheme 1 is the ability to engage carbenes from **A** in intramolecular cyclopropanation in preference to intramolecular β -hydride migration to give **E**.¹⁵ Bicyclobutane carboxylates were first prepared from ethyl α -allyl- α -diazoacetate in seminal work by Ganem.¹⁶ However, β -hydride migration was a significant side reaction. In recent years, our group¹⁵ and that of Hashimoto¹⁷ have developed intermolecular Rh-catalyzed transformations of α -alkyl- α -diazoesters that tolerate β -hydrogens, including reactions that produce cyclopropenes, cyclopropanes, dioxolanes, tetrahydrofurans and functionalized indoles. Low temperatures ($-78\text{ }^{\circ}\text{C}$) and bulky carboxylate ligands are key to the success and the dramatic suppression of β -hydride migration.¹⁵

Our success with intermolecular cyclopropanation led us to question if enantiomerically enriched bicyclobutanes could be prepared via intramolecular cyclopropanation. To develop a system that would function in subsequent homoconjugate addition reactions with Grignard reagents, we focused on the preparation of *tert*-butyl bicyclobutanecarboxylates which were expected to be resistant toward nucleophilic attack at the ester carbonyl. In the course of our studies, Davies¹⁸ very recently reported the first enantioselective intra-molecular cyclopropanation to yield bicyclobutanecarboxylates. In this elegant study, the catalyst $\text{Rh}_2(R\text{-BTCP})_4$ was used to achieve bicyclobutanation in 61–74% yield and up to 94% ee. Davies' system is most effective for methyl or ethyl (*E*)-2-diazo-5-arylpent-4-enoates. The method described herein is complementary, as it functions most efficiently with the corresponding *tert*-butyl esters as required for subsequent homoconjugate addition.

The development of an enantioselective bicyclobutanation procedure began with (*E*)-2-diazo-5-arylpent-4-enoates, which are readily prepared by alkylation of *t*-butyl acetoacetate with the cinnamyl halides and subsequent diazo transfer. Building on earlier experience with enantioselective intermolecular reactions of α -alkyl- α -diazoesters,¹⁵ we screened the bicyclobutanation of **1a** using dirhodium carboxylates with *N*-imido-*tert*-leucinate ligands.¹⁹ An optimization study (see Supporting Information) revealed that $\text{Rh}_2(S\text{-NTTL})_4$ in toluene at $-78\text{ }^{\circ}\text{C}$ is effective for bicyclobutane formation, providing (*S,S*)-**2a** in 83% yield, and 95% ee. As shown in Table 1, *tert*-butyl (*E*)-2-diazo-5-arylpent-4-enoates **1a–g** with aromatic halogen, CF_3 , nitrile, ester and ether substituents were productive substrates under $\text{Rh}_2(S\text{-NTTL})_4$ -catalyzed conditions to give bicyclobutane products in 76–88% yield and 91–95% ee. Bicyclobutane **2h**, with an *ortho*-methoxy substituent, was formed with high enantioselectivity (94% ee) but a more modest 65% yield. Likewise, the α -naphthyl substituted **2i** was formed in 90% ee and 67% yield. *tert*-Butyl (*E*)-2-diazo-6-phenylhex-4-enoate gave the benzyl substituted **2j** in 80% yield but 71% ee.

Comparison of the Rh-catalyzed reactions of alkene stereoisomers **1k** and **1l** provided mechanistic insight. The (*E*)-isomer **1k** gave bicyclobutane **2k** in 80% yield and 73% ee. In low yield (8% by ^1H NMR), the (*Z*)-isomer **1l** also gave **2k**, along with inseparable dienes from β -hydride migration. The stereoconvergent formation of **2k** rules out a concerted cyclopropanation mechanism for **1l**. It is likely that zwitterionic **F** is an intermediate from the reaction of **1l**, and possibly a common intermediate from the reaction of **1k**. Similarly, (*Z*)-alkene **1m** provided 15% of the bicyclobutane **2a**— the same diastereomer obtained from (*E*)-alkene **1a**. Again, the stereoconvergence supports a zwitterionic intermediate from

(*Z*)-alkene **1m**. Interestingly, the major product from **1m** was the Buchner product²⁰ (+)-**3**, obtained in 69% yield and 99% ee.

We next studied the addition reactions of **2a** with Grignard reagents (Table 2). The uncatalyzed addition of PhMgBr in Et₂O gave only traces of diastereomers **4** upon acidic quench (entry 1). Conditions of Gaoni¹² (CuI in Et₂O) gave **4** in only 8% yield (entry 2). Neither CuCN nor CuBr•SMe₂ promoted the reaction under similar conditions (entries 3,4). After a number of Cu-sources, ligands and solvents were screened, it was found that CuBr•SMe₂ (30 mol %), PBu₃ (1.2 equiv) and THF provide a catalyst system that is highly effective. When **2a** was combined for 30 min with two equivalents of PhMgBr or MeMgCl, cyclobutanes **4** and **5** were obtained in 88% and 90% yield, respectively. The same conditions with less MeMgCl (1.5 equiv) gave **5** in a somewhat lower 75% yield (entry 7). Likewise, **5** was obtained in 83% yield with less catalyst (10 mol % CuBr•SMe₂/40 mol % PBu₃), (entry 8). Given the low cost of the catalyst and nucleophiles, we continued with 30 mol % copper and 2 equiv of Grignard reagents.

As shown in Table 3, a one-flask, two-catalyst procedure was developed for the three-component preparation of enantiomerically enriched cyclobutanes from (*E*)-2-diazo-5-arylpent-4-enoates, Grignard reagents and electrophiles. While toluene was the best solvent for the bicyclobutanation, it was detrimental to the conjugate addition. Thus, a solvent swap was conducted by simply removing toluene *in vacuo* prior to the conjugate addition. In this manner, cyclobutane product **4** was obtained in 80% yield from **1a** and as a 1.1:1 epimer at the C1 position. With a subsequent step (15 h), **4** could be readily improved to 21:1 dr using catalytic *t*BuOK in THF. Other Grignard reagents such as MeMgCl, EtMgCl, BnMgCl, *p*-fluorophenylmagnesium bromide and *p*-methoxyphenylmagnesium bromide afforded cyclobutane products **5**, **11–14** in 68–82% yields. In each case, the product dr could be improved to 17:1 by epimerization with *t*BuOK. Substituted α-cinnamyl-α-diazoacetates were also tolerated by this one-flask procedure, as illustrated by the preparation of **15** and **16**. α-Diazoketone **1n** also participated in sequential bicyclobutanation/homoconjugate addition to give **17** in 60% yield, albeit in 34% ee.

As noted above, the diastereomer ratios obtained upon acidic quench differed from those obtained upon epimerization.^{14a} It was speculated that the sense of diastereoselectivity could be reversed by using BHT as a sterically demanding proton source (Scheme 2). Indeed, BHT quench gave **5** and **16** in 1:6 dr and 1:17 dr, respectively.

Upon conjugate addition, the resulting enolate products could also be directly quenched with electrophiles to provide cyclobutanes that contain quaternary stereocenters (Table 3). Electrophiles included allyliodide, EtI, BnBr, PhSSPh, and 4-bromobenzoyl chloride to give products **6–10** with 7:1 – 14:1 dr. X-ray crystallography established the absolute stereochemistry of **10** as well as the bicyclobutane precursor **2a**.

In conclusion, enantiomerically enriched cyclobutanes can be constructed by a 3-component, 2-catalyst, single-flask process in which (*E*)-2-diazo-5-arylpent-4-enoates are treated with Rh₂(*S*-NTTL)₄ to provide enantiomerically enriched bicyclobutanes. A subsequent sequence of Cu-catalyzed homoconjugate addition/enolate trapping provides highly substituted cyclobutanes with high diastereoselectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Multicomponent cyclobutane synthesis

Scheme 2.
Reversal of Diastereoselectivity

Table 1

Enantioselective Bicyclobutanation

^a ee determined for the alcohol from DIBAL reduction of **16**, Table 3.

^b Diene products from β -hydride migration predominated and were inseparable from **2k**. The yield of **2k** from **1l** was estimated by ^1H NMR.

Table 2

Optimization of homoconjugate addition

Entry	RMgX (equiv)	Cu(I) (equiv), time, solvent	T (°C)	Yield (%)
1	PhMgBr (2.0)	none, 5 h, Et ₂ O	r.t.	trace
2	PhMgBr (1.5)	CuI (1.5), 5 h, Et ₂ O	r.t.	8
3	PhMgBr (1.5)	CuCN (1.5), 5 h, Et ₂ O	r.t.	0
4	PhMgBr (1.5)	CuBr•SMe ₂ (1.5), 5 h, Et ₂ O	r.t.	0
5	PhMgBr (2.0)	CuBr•SMe ₂ (0.3) PBU ₃ (1.2), 30 min, THF	r.t.	88 1.1:1 dr
6	MeMgCl (2.0)	CuBr•SMe ₂ (0.3) PBU ₃ (1.2), 30 min, THF	r.t.	90 1.3:1 dr
7	MeMgCl (1.5)	CuBr•SMe ₂ (0.3) PBU ₃ (1.2), 30 min, THF	r.t.	75
8	MeMgCl (2.0)	CuBr•SMe ₂ (0.1) PBU ₃ (0.4), 30 min, THF	r.t.	83

Table 3

One-flask, multicomponent bicyclobutane synthesis

^aDetermined by $^1\text{H-NMR}$ analysis.^bEpimerization in separate experiment using $t\text{BuOK}$ (20 mol %), THF (0.1 M) for 15 h at r.t. proceeded in 88–98% yield.^cThe enantiomeric excess of the major diastereomer of **5** was confirmed to be 95% ee by chiral HPLC.

^d Determined ee with alcohol obtained by reducing **16** with DIBAL.