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B-Alkylcatecholborane-Mediated Tandem Radical Conjugated Addition−Aldol Cyclization

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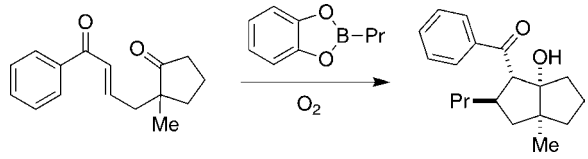
ABSTRACT



A one-pot procedure involving radical conjugate addition of *B*-alkylcatecholboranes to enones followed by intramolecular aldol reaction is reported. Application to the stereoselective synthesis of monocyclic and bicyclic products with up to four contiguous stereogenic centers is presented.

Formation of C−C bonds is a key process in synthetic organic chemistry. Running tandem processes involving more than one C−C bond formation is highly attractive since they allow a rapid increase in molecular complexity.[1] In recent years, we have explored the use of radical reactions in synthesis and have developed a wide range of C−C bond-forming radical reactions such as conjugate addition, allylation, alkynylation, and vinylation using organoboranes as radical precursors.[2,3] Interestingly, the radical conjugated addition reaction of organoboranes to various α,β-unsaturated ketones occurs via formation of boron enolates.[3,4] Since boron enolates are known to participate efficiently in aldol reactions, a tandem process involving a radical conjugate addition followed by an aldol reaction could be envisaged.[5,6] Tandem conjugate addition−aldol reactions using organometallic species are well documented in the literature.[7] Examples of radical mediated conjugated addition followed by an aldol processes involving boron[8] and zinc[9] enolate intermediates have been reported. In this communication, we describe a process involving efficient radical mediated conjugate additions of *B*-alkylcatecholboranes to enones

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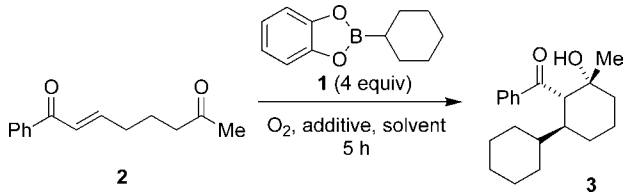
followed by stereoselective intramolecular aldol reactions.

Optimization of reaction conditions was performed by using *B*-cyclohexylcathecholborane **1** (4 equiv) and the α,β-unsaturated diketone **2** (Table 1).

Table 1. Optimization of the Conjugate Addition−Intramolecular Aldol Cyclization Process

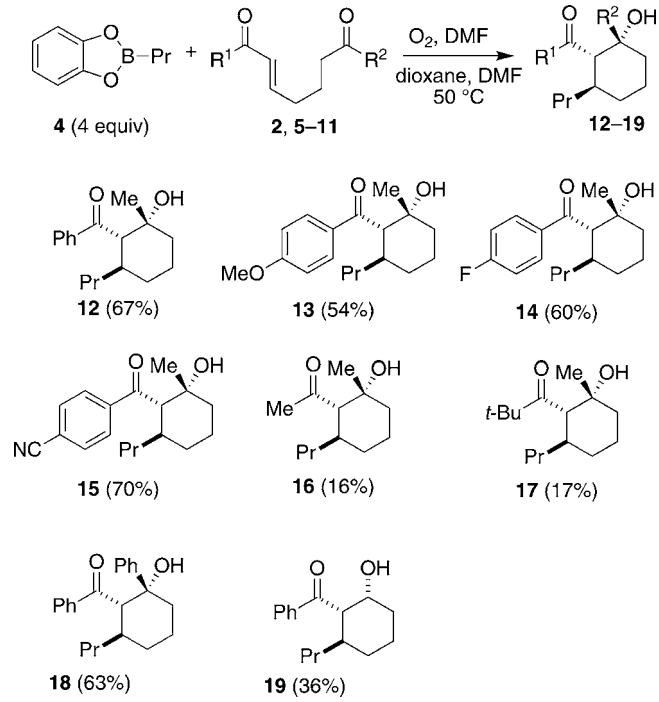


entry	solvent	additive (1.5 equiv)	temp [°C]	yield
1	CH_2Cl_2	-	35	38%
2	$ClCH_2CH_2Cl$	-	93	20%
3	THF	-	68	48%
4	dioxane	-	110	55%
5	dioxane	-	50	64%
6	dioxane	Et_3N	50	46%
7	dioxane	DMPU	50	60%
8	dioxane	DMF	50	74%

First, a preliminary screening of solvent at reflux was performed (Table 1, entries 1−4). The best yield (55%) for the formation of cyclohexanol **3** was obtained in dioxane. Decreasing the temperature at 50 °C resulted in a higher yield of 64% (entry 5), and further decrease of the reaction temperature had a slight negative influence on the yield and resulted in much longer reaction time. Since it has been shown that additives such as Et_3N,[10] DMPU,[3] and DMF[11] have a positive effect on radical reactions involving organoboranes, the effect of additive was investigated next (entries 6−8). Et_3N and DMPU have a negative effect on the yield; however, DMF afforded the aldol product **3** in an improved yield of 74% (entry 8).[12]

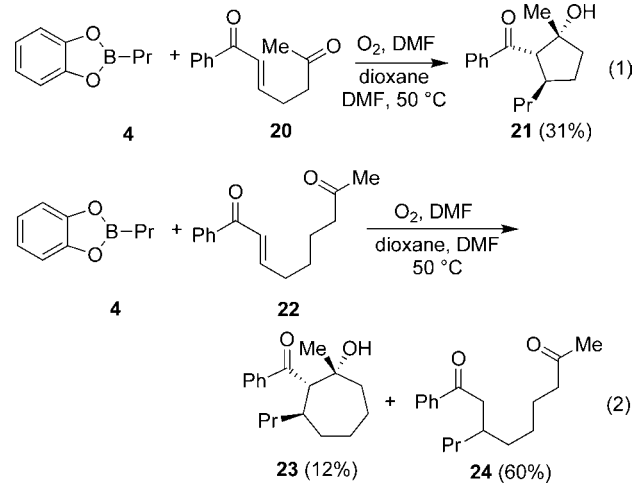
Representative tandem radical conjugated addition−aldol cyclizations leading to six-membered ring formation using commercially available propylcatecholborane **4** and different enones **2** and **5**−**11** under the aforementioned optimized conditions are presented in Scheme 1. Aromatic enones were tested first (R^1 = aryl), and yields between 54% (**13**, R^1 = *p*-OMe) and 70% (**15**, R^1 = *p*-CN) were obtained. Aliphatic

Scheme 1



enones **8** and **9** (R^1 = Me and *t*-Bu) gave the expected cyclohexanol derivatives **16** and **17** in low yields. Formation of the noncyclized products resulting from a simple conjugate addition was also observed. Finally, the nature of the keto group was investigated by varying R^2. Aliphatic (**2**, R^2 = Me) and aromatic (**10**, R^2 = Ph) gave similar yields of 67% (**12**) and 63% (**18**). Finally, the aldehydes **11** (R^2 = H) gave the cyclohexanol **19** in moderate yield (36%). All reactions depicted in Scheme 1 are fully stereoselective according to ^1H and ^{13}C NMR spectra of the crude products. The relative

Scheme 2



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(12) Optimized procedure for the preparation of **3**: under N_2, *B*-cyclohexycatecholborane (1.10 g, 5.6 mmol) and DMF (0.17 mL, 2.1 mmol) were added to a solution of the radical trap **2** (300 mg, 1.4 mmol) in dioxane (0.35 M). The reaction mixture was heated at 50 °C, and dry oxygen air (500 mL, 4.6 mmol O_2) ($CaCl_2$) was slowly bubbled into the solution. After 7 h, the reaction mixture was concentrated and flash chromatography afforded **3** (311 mg, 74%) as a single diastereomer (cyclohexane/*t*-BuOMe). White solid. Mp 86−87 °C.

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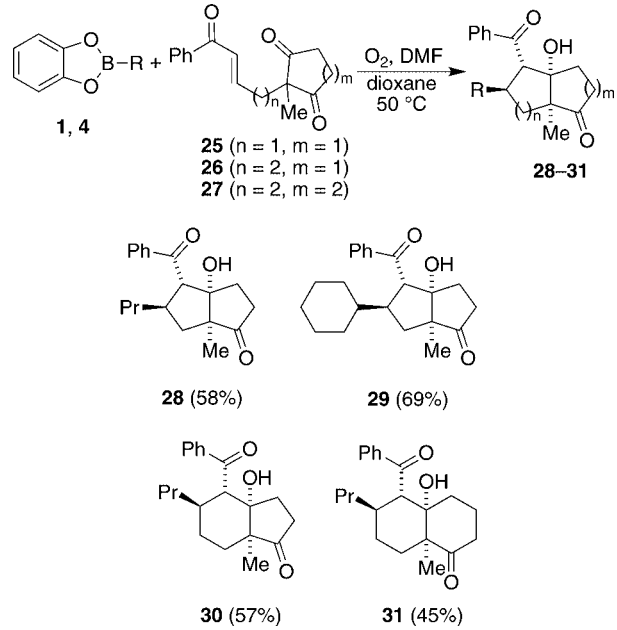
configuration of the products has been attributed by analogy of closely related compounds.[13]

The ring size was investigated next (Scheme 2). The formation of the five-membered ring **21** (eq 1) is possible; however, the yield is lower than for the six-membered ring **12** (31% vs 67%). The seven-membered ring **23** was obtained in low yield (12%) together with the product of conjugate addition **24** (60%) (eq 2).

The preparation of bicyclic systems starting from enones **25**−**27** and organoboranes **1** and **4** affords the bicyclic compounds **28**−**31** in 45% to 69% yield (Scheme 3). The

Scheme 3



reaction is highly diastereoselective, and only one diastereoisomer was detected and isolated for each reaction. The relative configuration of **30** and **31** has been established by single-crystal X-ray diffraction analysis (see Supporting Information).

From a mechanistic point of view, two pathways (**A** and **B**, Scheme 4) could be envisaged. In pathway **A**, the radical addition to the enone is followed by trapping of the enolate radical by the organoborane and formation of an intermediate boron enolate that can undergo an intramolecular aldol reaction. This mechanism is supported by the stereochemical outcome of the reaction where the OH and the acyl group are cis configured in accordance with similar intramolecular aldol reactions reported by Krische.[5,13] In the second mechanism, pathway **B**, cyclization of the enolate radical affords an intermediate alkoxyl radical that is trapped by the organoborane to deliver after hydrolysis the same cyclohexanol derivative.[14]

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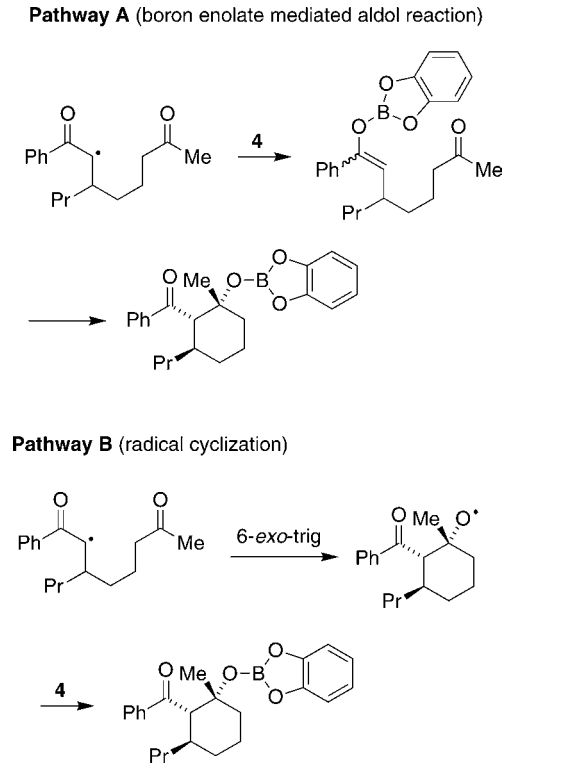
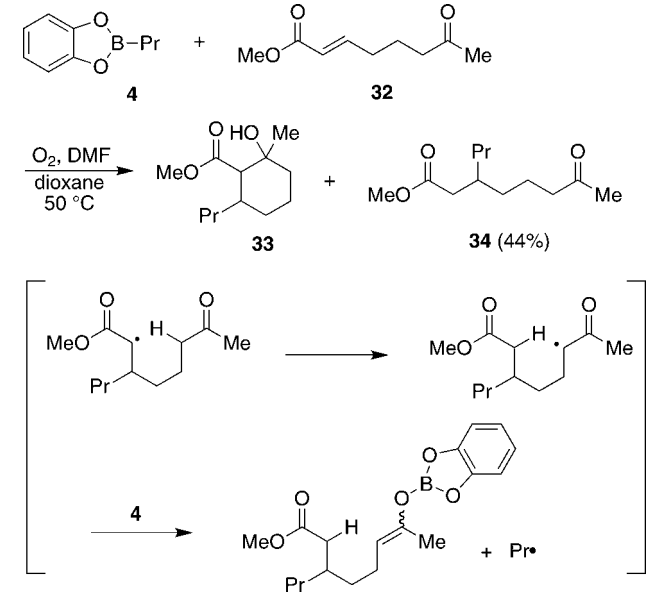
Scheme 4



If this second mechanism is occurring, it is expected that the reaction will also work with unsaturated esters such as **32**. Indeed, we have reported that ester enoyl radicals do not react with *B*-alkylcatecholborane to form a boron enolate, and therefore only the second pathway could lead to the cyclohexanol derivative **33**. By performing the reaction with **32** (Scheme 5), the acyclic ketoester **34** was isolated in 44%

Scheme 5



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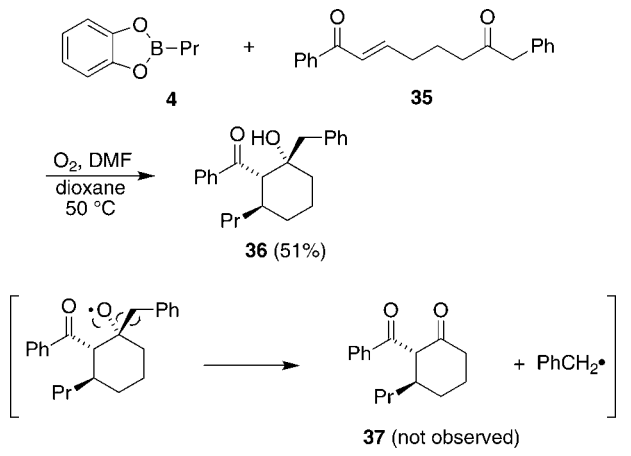
yield. No trace of cyclohexanol **33** was detected. Since conjugate addition of *B*-alkylcatecholborane to an unsaturated ester is not a chain process,[15] the 44% yield may result from a 1,5-hydrogen transfer according to Scheme 5.

A second mechanistic probe was investigated. The enedione **35** was allowed to react with **4** (Scheme 6). The

Scheme 6



cyclohexanol **36** was isolated in 51% yield as the only product. This result also supports the mechanistic hypothesis of pathway **A** involving a boron enolate since the radical cyclization should lead to an alkoxyl radical that is expected to fragment rapidly to the cyclohexanone derivative **37**. No trace of this ketone could be detected in the reaction. Therefore, we believe that the cyclization process involves a boron enolate according to pathway **A**.

In conclusion, we have developed a procedure for the formation of polysubstituted cyclohexanol derivatives involving a radical conjugate addition of *B*-alkylcatecholboranes to enones followed by an intramolecular aldol reaction. Diastereoselective synthesis of monocyclic and bicyclic β-hydroxyketones with up to four contiguous stereogenic centers has been achieved.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. X-ray crystallographic data for compounds **30** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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