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Brønsted Acid Catalyzed Homoconjugate Addition of Organotrifluoroborates to Arylated Cyclopropyl Ketones

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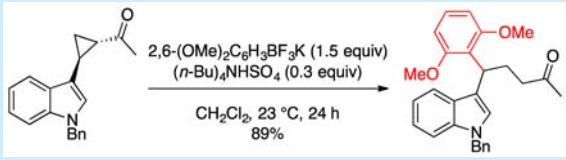
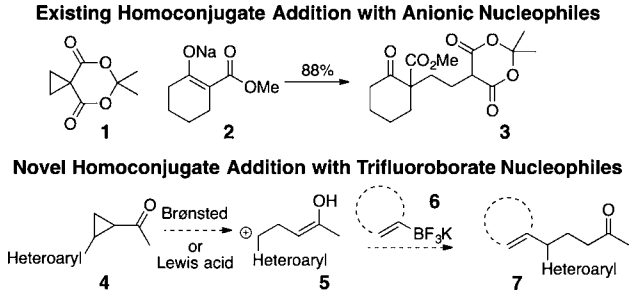
Supporting Information

ABSTRACT: A novel and practical homoconjugate addition of alkenyl, alkynyl, heteroaryl, and aryl trifluoroborates to arylated cyclopropyl ketones to synthesize γ,γ-disubstituted ketones is reported. A preliminary mechanistic proposal involving ketone protonation, an intermediary carbocation, and intermolecular nucleophile addition has been made based on control studies.



The homologation of reactions is a robust strategy to expand the utility of a given transformation, as it allows access to products with an additional CH_2 unit. Homologous enolate,[1] crotylation,[2] Nazarov,[3] Cope rearrangement,[4] and conjugate addition[5] reactions have been disclosed. In homoconjugate addition reactions for C−C bond formation,[6] anionic nucleophiles are typically added to cyclopropanes with two electron-withdrawing groups, taking advantage of "spiroactivation" as proposed by Danishefsky (Scheme 1).[5a−d,7] A

Scheme 1. Homoconjugate Additions



few examples of cyclopropanes activated by a single electron-withdrawing group have been reported. However, these either recapitulate spiroactivation via spirofused cyclopropyl ketones[5e] or take advantage of cyclopropanes contained within a highly strained bridged bicycle or bicyclo[1.1.0]butane system.[5e,8] Using a Lewis acidic nucleophile, perhaps generated from a boronate or trifluoroborate such as **6**, would allow acceptor/donor cyclopropanes[9] **4** to be used as substrates with intermediate carbocation formation.[5f] This strategy accommodates substrates with a single withdrawing group that do not need additional ring strain or spiroactivation, thus providing a significant expansion of substrate scope for homoconjugate additions.

In addition to their use as coupling partners,[10] organoboronates and borates have served as nucleophiles for allylations and crotylations,[11] conjugate additions,[12,13] Pestasis reactions,[14] and oxocarbenium additions.[15] An important benefit of using alkenyl, alkynyl, and aryl boronates and trifluoroborates is the broad functional group tolerance of these nucleophiles, including the use of unprotected heterocycles (see **4**). Our successful use of trifluoroborate-based nucleophiles in conjugate additions[12e] inspired this investigation for their use in homoconjugate additions to provide γ-functionalized ketones.

Reaction initiation could be promoted in theory by the use of Brønsted acid, Lewis acid, or iminium catalysis. We initially looked at Brønsted acids as cost-effective reagents. An initial screen of organic and inorganic acids (20 mol %) in dichloromethane showed the formation of adduct **9** in every case (Table 1, entries 1−5). $KHSO_4$ appeared to be the best acid for the reaction, outperforming the others by a factor of 4 or more. It appears that having an acid pK_a around 2 is optimal for reactivity. The use of a more soluble salt, with n-Bu_4N^+ as the cation, improved the outcome, especially when 30 mol % was used (Table 1, entries 6 and 7). Other solvents proved inferior to dichloromethane (Table 1, entries 8−9). Toluene worked similarly well at times, but not for all substrates. The use of boronic acids in the reaction did not give measurable amounts of products unless molecular sieves were used, and even then the product was obtained in a low yield (entry 10).[16]

Variation of the trifluoroborate nucleophile showed that the homoconjugate addition accommodates a wide range of alkenyl, alkynyl, heteroaryl, and aryl nucleophiles (Table 2). The addition of *para* substituents to the styrenyl trifluoroborate did not greatly affect the reactivity (see **11a−f**). The pentenyl borate reacted well to give **12**. Alkynyl nucleophiles were more sensitive to the acidic conditions, but still afforded adducts **13a−d** in useful yields. Aryl and heteroaryl nucleophiles were next examined. The γ,γ-biaryl products **14−16** show that both *para*- and *ortho*-substituted aryl nucleophiles reacted well. An unprotected phenolic hydroxyl created no problems (**16b**), nor

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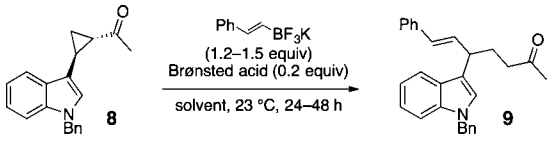
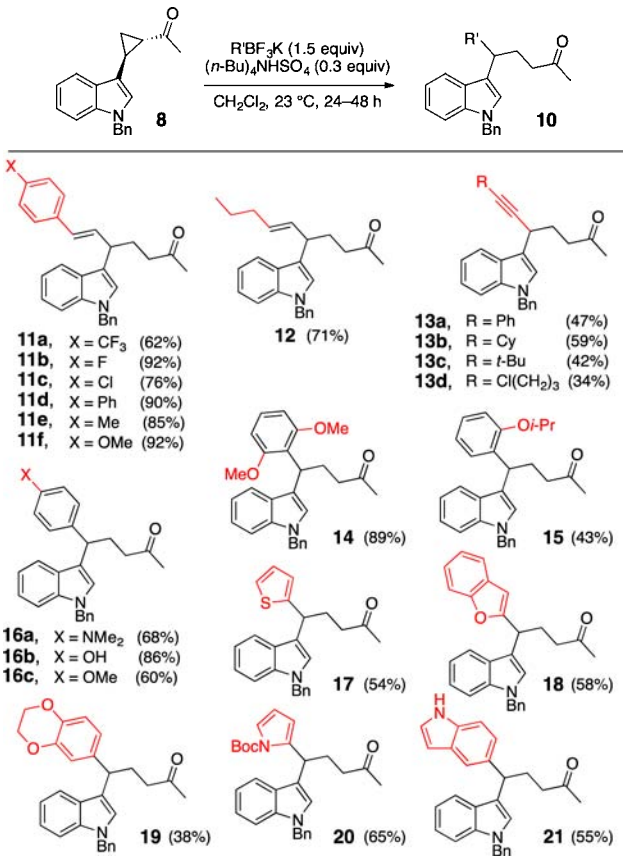
Table 1. Identifying Effective Reaction Conditions[16]



entry	acid (pK_a)[a]	solvent	yield (%)[b]
1	F_3CCO_2H (−0.26)	CH_2Cl_2	7[c]
2	Cl_2CHCO_2H (1.29)	CH_2Cl_2	13[d]
3	$KHSO_4$ (1.99)	CH_2Cl_2	87
4	H_3PO_4 (2.12)	CH_2Cl_2	23[d]
5	o-$(NO_2)C_6H_4CO_2H$ (2.17)	CH_2Cl_2	14[d]
6	Bu_4NHSO_4	CH_2Cl_2	89
7	Bu_4NHSO_4[e]	CH_2Cl_2	96
8	Bu_4NHSO_4	PhMe	90
9	Bu_4NHSO_4	THF	87
10	Bu_4NHSO_4	CH_2Cl_2	19[f]

[a] pK_a in H_2O.[17] [b] Isolated yield (average of 2 runs). [c] Yield based on integration in ^1H NMR relative to methyl 4-nitrobenzoate. [d] Starting material was recovered from the reaction. [e] 30 mol % used. [f] Boronic acid and 4 Å MS used.

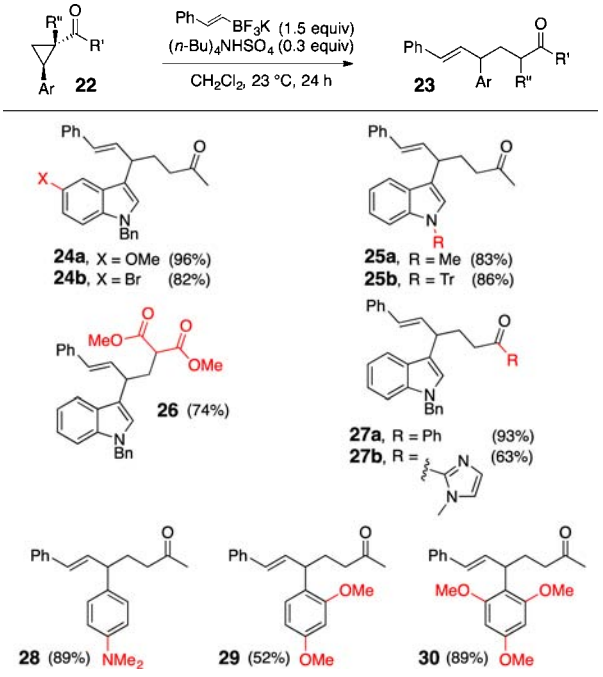
Table 2. Reaction Scope: Nucleophiles



did the steric hindrance of *o*,*o*-disubstitution (**14**). Heteroaromatics performed less well in the presence of acid, though **17**–**21** were obtained in useful yields.

The tolerance for substitution around the cyclopropane was next examined. Unfortunately, electron-poor aromatics or an unsubstituted phenyl group in place of the indole of **8** provided no products.[16] This is consistent with the hypothesized carbocationic intermediate. However, a range of electron-rich aromatics and heteroaromatics could be used with satisfactory results (Table 3). Substitution, including an electron-withdrawing group, could be made on the indole aryl ring (**24a**–**b**)

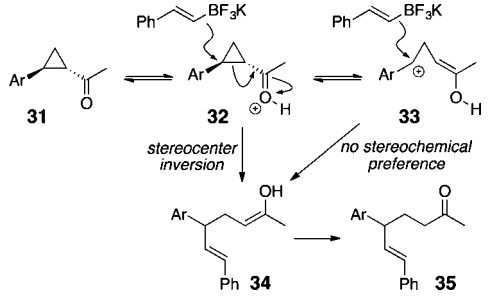
Table 3. Reaction Scope: Electrophiles



or on the nitrogen (**25a**–**b**) without any loss in reactivity. Diester-, phenylketone-, and acylimidazole-substituted cyclopropanes gave **26**, **27a**, and **27b**, respectively, without problems. The latter may be used as a synthetic equivalent for esters and amides.[18] Aryl cyclopropanes reacted well as long as electron-donating substituents were present. Again, *o*,*o*-disubstitution was not a problem, and ketones **28**–**30** were obtained in useful yields.

All of the substrates in the above-mentioned tables were obtained as racemic mixtures. Mechanistically, either a stereospecific mechanism where the nucleophile attacks the cyclopropane **31** to produce enol **34** (Scheme 2) with inversion

Scheme 2. Possible Reaction Mechanisms



at the point of attack or an initial cyclopropane fragmentation to the achiral cation **33** could be operative. Consequently, we ran an experimental control with enantioenriched cyclopropane **36** (Scheme 3). While the substrate was introduced to the reaction with an er of 81:19, the product was obtained as essentially a racemate. If the reaction was run to only partial completion (4, 8, or 12 h), loss of enatioenrichment in the starting material **34** from 81:19 er to 50.5:49.5 er was seen.[16] These data suggest that a rapid equilibration between

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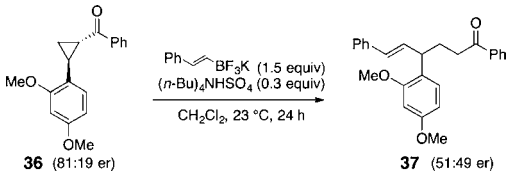
Scheme 3. Loss of Enantioenrichment



36 (81:19 er) **37** (51:49 er)

cyclopropane **32** and cation **33** occurs, followed by a much slower nucleophilic attack at the carbocation.

In light of the proposed mechanism, we believe a stereoablative[19] enantioselective version of this reaction will be possible. However, preliminary trials with typical chiral Brønsted acids showed no stereoinduction, and only racemic products were obtained.[16]

In conclusion, we report a novel and practical homoconjugate addition of alkenyl, alkynyl, heteroaryl, and aryl trifluoroborates to arylated cyclopropyl ketones to synthesize γ,γ-disubstituted ketones. A preliminary mechanistic proposal has been made based on control studies. Efforts to find conditions to effect an enantioselective transformation are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01795.

A full list of control experiments, reaction conditions examined, experimental procedures, and physical characterization may be found (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Please see the Supporting Information for a full list of control experiments, experimental details, and characterization data.

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