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Highly Diastereoselective Formal Nucleophilic Substitution of Bromocyclopropanes

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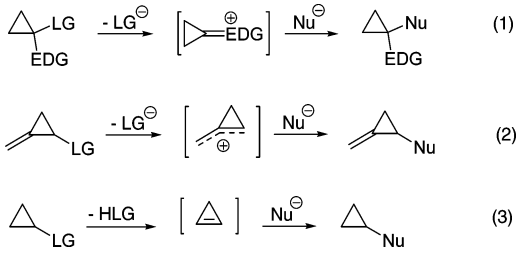
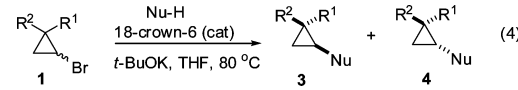
Donor−acceptor cyclopropanes (DACs) have found widespread application in organic synthesis as equivalents of C_3-electrophiles or all-carbon 1,3-dipoles.[1] A number of useful protocols employing DACs have been developed, including various nucleophilic additions,[2] [3 + 2],[3] [3 + 3],[4] and [3 + 4] cycloaddition reactions.[5] DACs are typically accessed via the catalytic cyclopropanation of enol ethers with carbenoids generated from diazoacetates[6] or via reaction of Fisher carbenes with electron-deficient olefins.[7] We envisioned an attractive, alternative approach for expeditious preparation of DACs via a direct reaction between appropriate nucleophiles and halocyclopropanes. While it is well-recognized that classical nucleophilic substitution in strained carbocycles is highly disfavored, it does occur for the substrates possessing strongly electron-donating geminal substituents (eq 1),[8] as well as in methylenecyclopropanes, assisted by the formation of an allylic carbocation (eq 2).[9] Alternatively, formal nucleophilic substitution can also be achieved via a 1,2-elimination to generate a cyclopropene intermediate, followed by addition of a nucleophile across the strained double bond (eq 3). The latter transformation proceeds readily in the presence of vicinal electron-withdrawing groups;[10] however, unsubstituted cyclopropyl halides have been shown to undergo this reaction as well, producing useful cyclopropanol[11] and cyclopropylamine[12] derivatives. However, the majority of the known reactions of this type (eq 3) either are nonselective due to harsh reaction conditions or have no potential selectivity issues, with only a handful of examples showing good site- or facial differentiations in polycyclic substrates where selectivity of addition is imparted by excessive rigidity and bulk.[13] Herein we wish to report a novel, general protocol for the highly diastereoselective inter- and intramolecular formal substitution of bromocyclopropanes with a wide range of oxygen- and nitrogen-based nucleophiles.



In the course of optimization of the 1,2-dehydrohalogenation reaction of bromocyclopropane **1a** (dr 1.2:1) en route to 3-methyl-3-phenylcyclopropene (**2a**),[14] we observed formation of notable amounts of *tert*-butoxide adduct **3aa** (eq 4, R^1 = Ph, R^2 = Me). Apparently, alkoxycyclopropane **3aa** was produced via a side process involving addition of the alkoxide across the double bond of **2a**. Remarkably, the addition proceeded with very high facial selectivity, producing a single *trans*-diastereomer **3aa**.[15] Further studies revealed that alkoxycyclopropane **3aa** can be obtained as the sole product in excellent yield when the reaction is allowed to run overnight at 80 °C (Table 1, entry 1). Similarly, the reaction of bromocyclopropane **1b**, bearing an ethyl substituent, provided *tert*-butyl ether **3ba** in high yield (entry 2). Diastereoselectivity of the *tert*-butoxide addition was controlled by steric factors, ensuring the nucleophile approach from the least hindered face (i.e., *cis* to alkyl substituent R^2). Inspired by this result, we rationalized that other, more nucleophilic species should easily outcompete *tert*-butoxide in the addition reaction.

Table 1. Formal Nucleophilic Substitution of Bromocyclopropanes



no	$R^1(R^2)$[a]	Nu[b]	product	yield, %[c]	dr **3**:**4**[d]
1	Ph	*t*-BuO[h]	**3aa**	93	>25:1
2	Ph(Et)	*t*-BuO[h]	**3ba**	85	>25:1
3	Ph	*n*-PrO	**3ab**	99	16:1
4	Ph	*i*-PrO	**3ac**	96	18:1
5	Ph	$Me_2NCH_2CH_2O$	**3ad**	83	11:1
6	Ph	*E*-MeCH=CHO[e]	**3ae**	98	>25:1
7	Ph	$PhCH_2O$	**3af**	75	>25:1
8	Ph	Ac(Me)N	**3ag**	85	13:1
9	Ph	*p*-MeC_6H_4O	**3aa**	70[i]	>25:1
10	*o*-$HOC_6H_4CH_2NHCH_2$	*t*-BuO[h]	**4ca**	69	>25:1
11	$CONEt_2$	*t*-BuO[h]	**4da**	87	1:20
12	$CONEt_2$	*n*-PrO	**4db**	94	1:14
13	$CONEt_2$	*n*-BuO	**4dh**	91	1:14
14	$CON(CH_2CH_2)_2$	CH_2=$CH(CH_2)_3O$	**4ei**	92	1:20
15	$CONHC_8H_{17}$-*n*	*n*-PrO	**4fb**	94	<1:25
16	$CONHC_6H_{13}$-*n*	*i*-PrO	**4gc**	91	<1:25
17	CONHBu-*t*	*t*-BuO[h]	**4ha**	92	<1:25
18	$CONHCHPh_2$	*t*-BuO[h]	**4ia**	75	<1:25
19	CONHBu-*t*(H)	*t*-BuO[h]	**3ja**	69	10:1
20	CO_2K[f]	*t*-BuO[h]	**4ka**	79	<1:25
21	CO_2K[g]	*t*-BuO[h]	**4la**	81	<1:25
22	CO_2K[f]	*n*-PrO	**4kb**	83	<1:25
23	$CON(CH_2CH_2)_2$	*N*-pyrrolyl	**4ej**	85	1:14

[a] R^2 = Me, unless specified otherwise. [b] Conditions: 18-crown-6 (10 mol %), *t*-BuOK (1.5−2.0 equiv), Nu-H (1.5−2.0 equiv), THF (0.1−0.2 M). [c] Isolated yields. [d] Determined by ^{1}H NMR of the crude reaction mixtures. [e] Allyl alcohol was used as a pronucleophile. [f] Quenched with MeI prior to isolation. [g] Quenched with allyl bromide prior to isolation. [h] *t*-BuOK (2.5−3.5 equiv total) was employed. [i] Only trace amounts of aryl ether **3ak** were detected by GC analysis of the crude mixture.

To test this idea, we carried out the reaction of **1a** in the presence of 1.5 equiv of *t*-BuOK with various pronucleophiles (eq 4, Table 1). We were pleased to find that both primary and secondary alkoxides underwent efficient addition, providing the corresponding cyclopropyl ethers **3ab** and **3ac** in high yields and excellent diastereoselectivities (Table 1, entries 3 and 4). Functionalized *O*-nucleophiles were also successfully employed in this transformation. 2-(Dimethylamino)ethanol reacted uneventfully affording **3ad** in very high yield (entry 5). Reaction of **1a** with allyl alcohol was accompanied with a base-assisted migration of the double bond providing potentially deprotectable[16] vinyloxycyclopropane **3ae** as the only product (entry 6). Benzyl-protected[17] cyclopropanol **3af** was also obtained in good yield (entry 7). Addition of a nitrogen-based nucleophile, *N*-methylacetamide, also proceeded smoothly

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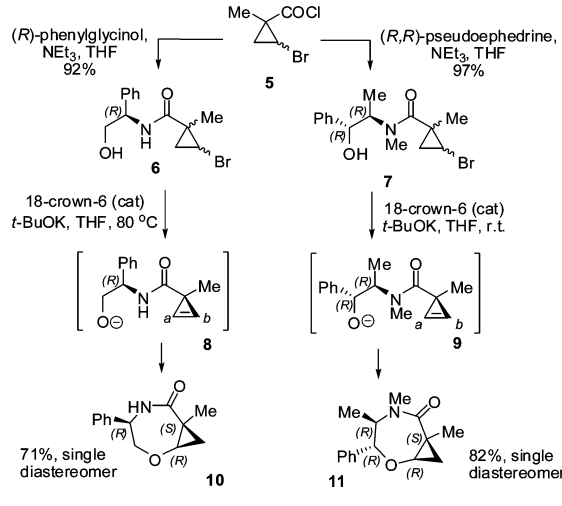
producing cyclopropylamine derivative **3ag** (entry 8). It should be emphasized that all the above-mentioned additions to **1a** performed in the presence of pronucleophiles (entries 3−8) occurred with perfect chemoselectivity and very high diastereoselectivity, which was controlled by steric factors. Considering the relatively high nucleophilicity of phenoxides,[18] we also attempted the reaction between *p*-methoxyphenol and **1a**. Surprisingly, only traces of arylcyclopropyl ether **3ak** were detected in the crude reaction mixture; instead *tert*-butoxide adduct **3aa** was obtained as the major product (entry 9).[19] An attempt to add a phenoxide species in an intramolecular fashion was also made (entry 10). Nonetheless, addition of *tert*-butoxide took place providing **4ca** as a sole product. Furthermore, it was found that the 2-(aminomethyl)phenolate moiety in **1c** served as a very efficient directing group exclusively producing the *cis*-diastereomer of **4ca** (entry 10). The reactivity of other functionalized bromocyclopropanes was tested next (Table 1, entries 11−23). It was found that both tertiary and secondary amides served as excellent directing groups, governing the addition of nucleophiles from the more hindered face. Thus, adducts with primary (**4db**, **4dh**, **4ei**, **4fb**), secondary (**4gc**), and tertiary alcohols (**4da**, **4ha**, **4ia**) were obtained in high yields and perfect *cis*-selectivity (entries 10−18). However, the reaction between *tert*-butoxide and enolizable carboxamide **1j** afforded the product of conjugate addition **3ja** with the thermodynamically more favorable *trans*-configuration (entry 19).[19] Although strongly nucleophilic reaction conditions did not permit employment of ester-containing substrates,[14b] the corresponding diastereomeric potassium 1-methyl-2-bromocyclopropylcarboxylates could efficiently be used instead (entries 20−22). Subsequent treatment of the resulting alkoxycarboxylates with methyl or allyl halide provided esters **4ka**, **4kb**, and **4la**, respectively, in good overall yields. Finally, pyrrole was successfully employed as an *N*-pronucleophile affording *cis*-*N*-pyrrolyl adduct **4ej** (entry 23). To further showcase the synthetic potential of this methodology, we explored intramolecular addition of tethered chiral alcohols en route to nonracemic bicyclic products (Scheme 1). Acylation of chiral amino alcohols with a racemic acyl

Scheme 1



chloride **5** provided amides **6** and **7** as mixtures of four diastereomers, which were subjected to the dehydrobromination conditions. Gratifyingly, both reactions exhibited perfect site selectivity: the intramolecular nucleophilic attack of the alkoxides in the cyclopropene intermediates **8** and **9** proceeded at only one of the diastereotopic sp^2-carbon atoms (*a*), efficiently producing the corresponding bicyclic oxazepinones **10** and **11** as sole products.[20]

In conclusion, a highly diastereoselective formal nucleophilic substitution of functionalized bromocyclopropanes with a wide range of oxygen- and nitrogen-based nucleophiles has been developed. It was shown that the selectivity in this reaction can be efficiently controlled by steric factors, by the directing effect of an appropriate functional group, or via a thermodynamically controlled isomerization. The application of this methodology to the expeditious synthesis of optically active bicyclic oxazepinones has been demonstrated.

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Supporting Information Available: Experimental details, procedures for preparation of starting materials, ^{1}H and ^{13}C NMR spectral charts, and X-ray structure for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) See Supporting Information for assignment of configurations by ^{1}H NOE NMR and X-ray crystallography.

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