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Chiral 1,2,3-Triazoliums as New Cationic Organic Catalysts with Anion-Recognition Ability: Application to Asymmetric Alkylation of Oxindoles

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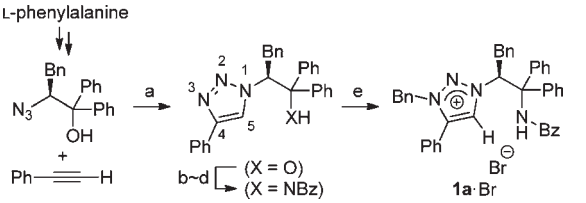
Supporting Information

ABSTRACT: Chiral 1,2,3-triazoliums have been designed, and the rational structural modification based on their unique anion-binding abilities has led to the establishment of the highly enantioselective alkylation of 3-substituted oxindoles.

Increasing attention has recently been directed toward 1,2,3-triazole derivatives as a result of their ready accessibility and unique properties.[1] In particular, 1,4-disubstituted 1,2,3-triazoles can be assembled in a facile manner by the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of terminal alkynes with organic azides, which represents one of the prime examples of click chemistry.[2] Stimulated by its high efficiency, regioselectivity, and functional group compatibility, Huisgen cycloaddition has been widely applied to the construction of organic and bioorganic molecular architectures.[3] Consequently, the intriguing properties of triazoles have been investigated closely in various fields of chemical science. In bioorganic systems, 1,4-disubstituted 1,2,3-triazole rings have been shown to serve as amide/peptide bond mimics, where the N(3) atoms of triazoles act as hydrogen bond acceptors and the polarized C(5) protons behave as hydrogen bond donors.[4] This function of C(5) protons has also been exploited in the area of supramolecular chemistry; synthetic molecules embedded with 1,2,3-triazole motifs are known to recognize anions through an array of C(5)−H···anion hydrogen bonds.[1c,5] Further, the anion binding capacity can be enhanced by converting a triazole unit to a triazolium cation possessing strongly increased CH-acidity.[6] Although these characteristic features of 1,2,3-triazoles and triazoliums would provide an attractive platform for the rational design of anion-recognizable chiral molecular catalysts, this possibility has remained unexplored.[7,8] Herein, we report the development of a chiral 1,2,3-triazolium salt of type **1** (Scheme 1) and its successful application to establish the highly enantioselective alkylation of 3-substituted oxindoles.[9]

Our strategy for the molecular design was based on two crucial synthetic sequences: (1) construction of the requisite 1,2,3-triazole core from a terminal alkyne and a chiral azide alcohol, a key building block readily accessible from the parent α-amino acid; (2) introduction of amide functionality via the displacement of the hydroxyl group with an appropriate nitrogen source such as an azide (Scheme 1). One of the advantages of this structural motif is that the triazolium cation would be tightly associated with the anion through electrostatic interaction and two hydrogen bonds, i.e., a C(5)−H···anion and a suitably positioned amide N−H···anion, to form a structured ion pair. The latter hydrogen bond might also play an important role in restricting the N(1)−C bond rotation. The actual assembly of the triazolium salt **1a**·Br was carried out by the operationally simple procedures from phenylacetylene and L-phenylalanine-derived azide alcohol.[10] It should be emphasized that another advantage of **1** is the numerous possibilities of structural modifications that can be easily made in the course of integrated synthesis using ordinary reagents and conditions, thus providing sufficient molecular complexity to build a large library of chiral 1,2,3-triazoliums.

Scheme 1. Synthesis of Chiral 1,2,3-Triazolium Salt 1a·Br[a]



[a] Reagents and conditions: (a) $CuSO_4 \cdot 5H_2O$ (30 mol %), Na ascorbate (60 mol %), *t*-BuOH/H_2O, 80 °C, 83%; (b) NaN_3 (5 equiv), TFA/TfOH, 0 °C; (c) Zn (2 equiv), HCO_2NH_4 (2 equiv), EtOAc/MeOH, rt; (d) BzCl (3 equiv), Py, rt, 95% over three steps; (e) BnBr (3 equiv), MeCN, reflux, 61%.

After an ion-exchange process, the three-dimensional molecular structure of **1a**·Cl was unambiguously determined by single-crystal X-ray diffraction analysis (Figure 1). As expected, the chloride anion was located in proximity to the triazolium C(5)−H proton and the amide N−H proton, thus being able to interact with them via double hydrogen bonding.[11] Further, because of the contribution of the amide unit to anion recognition, the directions of the substituents on the stereogenic N(1)−C carbon could be regulated to create a discrete chiral environment around the anion. The additional evidence for the double hydrogen-bonding interactions came from the ^{1}H NMR spectra of **1a** paired with various counteranions (**1a**·BF_4, **1a**·Br, **1a**·Cl, and **1a**·OAc) measured in dichloromethane-d_2 (Figure 2). With an increase in the Brønsted basicity of the anions, significant yet simultaneous downfield shifts were observed for the triazolium C(5) proton *a* and amide proton *b*,[12] indicating that both of the protons were strongly bound to the anion.

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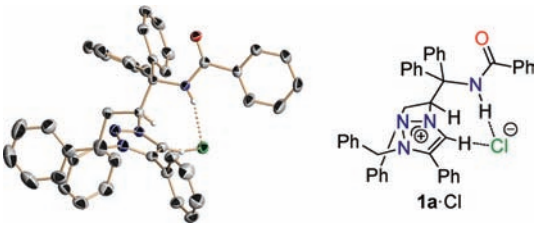


Figure 1. ORTEP diagram of **1a**·Cl (calculated hydrogens and solvent molecules are omitted for clarity).

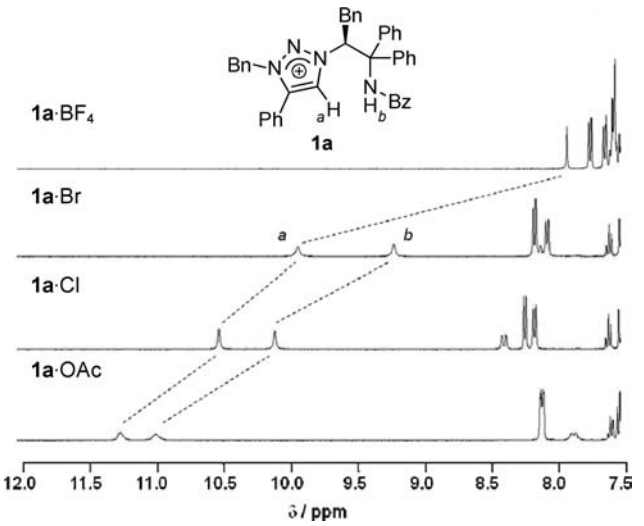
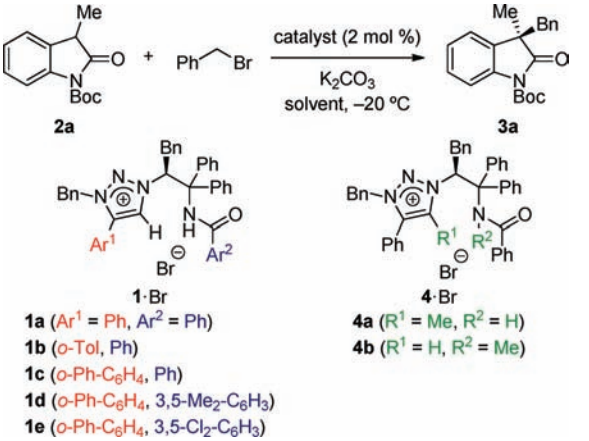


Figure 2. Partial ^{1}H NMR spectra of **1a**·BF_4, **1a**·Br, **1a**·Cl, and **1a**·OAc in CD_2Cl_2 (0.01 M) at 293 K.

With the exact structure of **1a** and definitive information regarding its anion-recognition ability in hand, we next focused on the exploration of its potential as an organic molecular catalyst for synthetically valuable carbon−carbon bond-forming reactions. For this purpose, we chose the asymmetric alkylation of oxindoles, i.e., construction of the quaternary carbon stereocenter at the C-3 position, because the 3,3-disubstituted oxindole framework is the ubiquitous structural core of many natural alkaloids and pharmaceuticals.[13] The initial trial of the benzylation of *N*-Boc-protected 3-methyloxindole **2a** was performed with 2 mol % of **1a**·Br and K_2CO_3 powder in dichloromethane at −20 °C, affording the desired product **3a** with moderate enantioselectivity (Table 1, entry 1). It should be noted that an attempted reaction with either C(5)-methyltriazolium salt **4a**·Br or *N*-methylbenzamido triazolium salt **4b**·Br as a catalyst under otherwise identical conditions resulted in the formation of nearly racemic **3a** (entries 2 and 3), confirming the importance of the double hydrogen-bonding interactions in asymmetric induction. Subsequent thorough investigations of the solvent effect on the reactivity and selectivity revealed that ethyl acetate was a solvent of choice for this alkylation (entry 4). We then pursued structural modifications of chiral 1,2,3-triazolium **1** by exploiting its modularity to improve the stereoselectivity. On the basis of the molecular structure of **1a**·Cl uncovered by the X-ray crystallographic analysis, we assumed the substituents at C-4 of triazolium (Ar^1) and at amide carbonyl (Ar^2) to be located in the vicinity of the prochiral enolate anion, thus exerting a crucial influence on the stereodetermining step. According to this assumption, the C(4)-phenyl substituent was replaced by the *o*-tolyl group (**1b**·Br), which indeed led to a notable improvement in the enantioselectivity (entry 5), and a satisfactory level of enantiocontrol was attained using **1c**·Br possessing a *o*-biphenyl substituent at C-4 as a catalyst (entry 6). Interestingly, the introduction of a 3,5-disubstituted phenyl group into the amide moiety delivered further enhancement of the enantiomeric excess (entries 7 and 8), and we found that the reaction proceeded smoothly in the presence of **1e**·Br to give **3a** almost quantitatively with 97% ee.

Table 1. Effect of Substitutents of 1 for Asymmetric Alkylation of Oxindole 2a[a]



entry	catalyst	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	**1a**·Br	CH_2Cl_2	48	69	58
2	**4a**·Br		48	65	−4
3[d]	**4b**·Br		48	72	9
4	**1a**·Br	EtOAc	12	85	56
5	**1b**·Br		12	99	84
6	**1c**·Br		12	99	93
7	**1d**·Br		12	96	95
8	**1e**·Br		12	99	97

[a] Reactions were carried out with 0.2 mmol of **2a**, 0.24 mmol of benzyl bromide, 0.5 mmol of K_2CO_3, and 2 mol % of **1**·Br or **4**·Br in 600 μL of solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] **4b**·Br is a mixture of amide conformers in a ratio of 1.3:1.

Experiments were then conducted to investigate the substrate generality of **1e**·Br-catalyzed asymmetric alkylation and the representative results are summarized in Table 2. In the reaction of oxindole **2** with a simple benzyl bromide, various C(3) alkyl substituents were well accommodated and excellent enantioselectivities were uniformly observed (entries 1−3). This benzylation was also applicable to 5-Me- and 5-MeO-oxindoles, **2e** and **2f**, without loss in enantiocontrol (entries 4 and 5). The construction of stereogenic quaternary carbon centers bearing allylic and propargylic substituents on **2f** could be achieved in a similar manner (entries 6−8). In this investigation, the absolute configuration of the allylated product **3g** was established to be *R* by comparing its optical rotation with that of a known enantiomer after removing the *N*-Boc group,[14] and the stereochemistry of the remaining examples were assumed by analogy. With benzylic bromides, the present system tolerated the incorporation of both electron-withdrawing and electron-donating substituents (entries 9−11). Moreover, bromoacetate appeared to be a good candidate for an electrophilic partner (entry 12).

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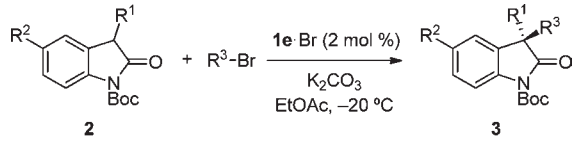
Table 2. Substrate Scope[a]



2b (R^1 = Et, R^2 = H) **2e** (R^1 = Me, R^2 = Me)
2c (R^1 = *i*-Pr, R^2 = H) **2f** (R^1 = Me, R^2 = OMe)
2d (R^1 = $CH_2CH{=}CH_2$, R^2 = H)

entry	2	R^3—Br	time (h)	yield[b] (%)	ee[c] (%)	3
1	**2b**	BnBr	8	82	98	**3b**
2	**2c**		72	87	97	**3c**
3	**2d**		8	98	97	**3d**
4	**2e**		18	99	98	**3e**
5	**2f**		18	96	95	**3f**
6	**2f**	$CH_2{=}CHCH_2Br$	10	92	90	**3g**
7	**2f**	$CH_2{=}CMeCH_2Br$	10	90	97	**3h**
8	**2f**	$CH{\equiv}CCH_2Br$	24	89	85	**3i**
9	**2f**	*p*-Br-$C_6H_4CH_2Br$	18	92	98	**3j**
10	**2f**	*p*-Me-$C_6H_4CH_2Br$	10	99	97	**3k**
11	**2f**	*m*-MeO-$C_6H_4CH_2Br$	24	94	97	**3l**
12	**2f**	MeO_2CCH_2Br	10	99	85	**3m**

[a] Reactions were conducted on a 0.2 mmol scale with 2 mol % of **1e**·Br, 0.24 mmol of alkyl halide, and 0.5 mmol of K_2CO_3 in 600 μL of EtOAc at −20 °C. [b] Isolated yield. [c] The enantiomeric excess of **3** was analyzed by chiral HPLC.

In conclusion, we have designed chiral 1,2,3-triazolium **1**, and its potential as a cationic organic catalyst has been demonstrated in the application to the asymmetric alkylation of 3-substituted oxindoles. We believe that judicious use of the structural modularity and anion-recognition ability of chiral triazolium cations of type **1** can offer a new yet fruitful opportunity for the rational molecular design and synthetic application of chiral organic ion-pair catalysts.

■ ASSOCIATED CONTENT

Supporting Information. Representative experimental procedures, spectral and analytical data for all new compounds, and crystallographic data for **1a**·Cl (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Triazolium C(5) proton *a* and amide proton *b* of **1a**·BF_4, **1a**·Br, **1a**·Cl, and **1a**·OAc were assigned by C—H COSY NMR analysis, respectively.

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