ORGANIC LETTERS

2012
Vol. 14, No. 7
1858–1861

Organocatalysis as a Safe Practical Method for the Stereospecific Dibromination of Unsaturated Compounds

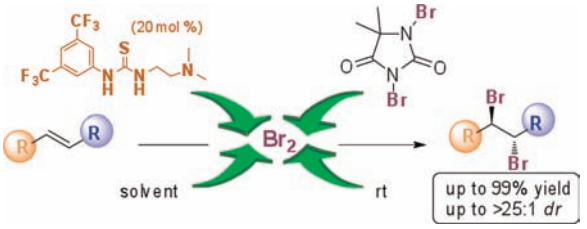
Gloria Hernández-Torres,[†,‡] Bin Tan,[†] and Carlos F. Barbas III*[,†]

The Skaggs Institute for Chemical Biology and Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 Torrey Pines Road, La Jolla, California 92037, United States, and Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

carlos@scripps.edu

Received February 23, 2012

ABSTRACT



Organocatalytic stereospecific dibromination of a wide variety of functionalized alkenes was achieved using a stable, inexpensive halogen source, 1,3-dibromo 5,5-dimethylhydantoin, and a simple thiourea catalyst at room temperature. The presence of a tertiary amine enhanced the rate of the dibromination reaction, and yields were good in various solvents, including aqueous solvents. The procedure was extended to alkynes and aromatic rings and to dichlorination reactions by using the 1,3-dichloro hydantoin derivative.

Halogenated compounds are important intermediates in syntheses of many natural product derivatives.[1] Many halogenated marine natural products are of pharmacological interest, and organic halides are useful synthons for chemical transformations such as substitutions and cross-coupling reactions. Certain organic halides are intermediates in the industrial-scale manufacture of pharmaceuticals, agrochemicals, and fine chemicals. Bromination of unsaturated C−C bonds has been primarily performed by using molecular bromine as a reagent, mainly in chlorinated solvents and under harsh reaction conditions.[2] During the past 10 years, several dibromination methods have been developed using more environmentally benign bromination reagents.[3] In these alternative protocols, other problematic substances are often used, however.[4] The most general methods for electrophilic bromination of alkenes employ a carrying agent supporting bromine[5] or in situ bromine generation that usually requires metal

[†] The Scripps Research Institute.
[‡] Universidad Autónoma de Madrid.

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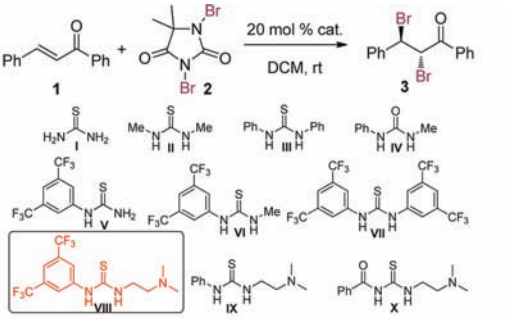
10.1021/ol300456x
Published on Web 03/23/2012

catalysts.[3k,l,6] Dibromination products are usually obtained as byproducts during halofunctionalization processes when *N*-bromosuccinimide (NBS) is used as a brominated agent.[7] Dibromination reactions using NBS usually require the presence of inorganic bromide salts such as LiBr.[8] Most organocatalytic halogenation procedures recently described are based on organocatalytic monohalogenation reactions, mainly asymmetric halolactonization processes, where the organocatalyst directs the chirality-determining step.[9] To the best of our knowledge, only one organocatalyzed dibromination of alkenes has been described;[10] this procedure uses pyrrolidine as a catalyst and a combination of NBS and succinimide. Halogenated solvent ($CHCl_3$) and high temperatures (60 °C) were required, and moderate to good yields of the *anti*-dibrominated product were obtained. The enantioselective version of this reaction using chiral pyrrolidine was unsuccessful. Asymmetric olefin dihalogenation remains a challenge. Nicolaou et al. developed a pioneering enantioselective dichlorination[11] of allylic alcohols catalyzed by a dimeric cinchona alkaloid to yield enantio-enriched *trans*-dichlorinated product.[12] The method requires preparation of aryl iododichlorides from PhI and hazardous Cl_2 gas. The ee's obtained were moderate.

Herein we report a new synthetic technique for dibromination of unsaturated C−C bonds founded on the unusual properties of hydantoin derivatives[13] when combined with a thiourea-functionalized catalyst. Mild conditions and no hazardous reaction components were used, and only inert byproducts were generated.

Table 1. Dibromination Catalyst Screen[a]



entry	catalyst	time(h)	conversion (%)	dr[b]	yield[c] (%)
1	I	5	100	10:1	86
2	II	24	85	>25:1	71
3	III	24	100	10:1	91
4	IV	36	NR	-	-
5	V	12	100	12:1	91
6	VI	36	91	12:1	76
7	VII	24	80	15:1	73
8	**VIII**	**3**	**100**	**>25:1**	**94**
9	IX	10	100	20:1	89
10	X	10	100	>25:1	92
11	X + Et_3N	0.5	100	>25:1	93
12	II + Et_3N	0.5	100	>25:1	94

[a] Reactions were carried out using **1** (0.2 mmol) and DBDMH **2** (0.4 mmol) in DCM (2 mL) with 20 mol % of catalyst at rt. [b] Determined by ^{1}H NMR of crude product. [c] Isolated yields.

Initial experiments were performed in dichloromethane (DCM) at rt using chalcone **1** as a model substrate with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a bromine source. The *anti*-selective dibromination reaction took place with excellent diastereoselectivity using 2 equiv of DBDMH and 20 mol % of a broad selection of thiourea derivatives as catalysts (Table 1). With simple thiourea **I**, the *trans*-brominated compounds were formed with good yields (86%) but moderate diastereoselectivity (10:1 dr). Using methyl and aryl substituted thiourea catalysts (**II**, **III**, **VI** and **VII**), the *trans*-brominated compounds were formed but low conversion rates were observed even with extended reaction times. Of these substituted catalysts, only the symmetric *N*,*N*′-dimethylthiourea catalyst **II** gave the product with excellent diastereoselectivity (> 25:1 dr). No product was obtained in the presence of urea derivative **IV**. As nucleophilic organocatalysts can substantially accelerate the transfer of electrophilic bromine from NBS to alkenes,[14,9b] we focused our study on thiourea derivatives containing tertiary amine moieties in their structure. Using thiourea catalyst (**VIII**−**X**), the *trans*-brominated compounds were formed with high diastereoselectivity (up > 25:1 dr) and excellent yields (89 to 94%). Thiourea catalyst **V** lacking the ethylenedimethylamine moiety but containing instead a free amine gave the dibrominated product in excellent yields but with lower diastereoselectivity (up to 12:1). It is noteworthy that, in the absence of

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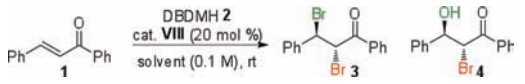
Table 2. Dibromination Solvent Screen[a]



entry	solvent	time (h)	yield **3** (%)[b]	dr of **3**[c]	yield **4**[b]
1	toluene	12	95	>25:1	–
2	DCM	3	94	>25:1	–
3	$CHCl_3$	1.5	93	>25:1	–
4	EtOAc	2	90	12:1	–
5	1,4-dioxane	2	79	>25:1	–
6	acetone	0.5	–	–	81
7	MeCN	1	55	7:1	–
8	H_2O/DCM (3:1)	1	82	9:1	–

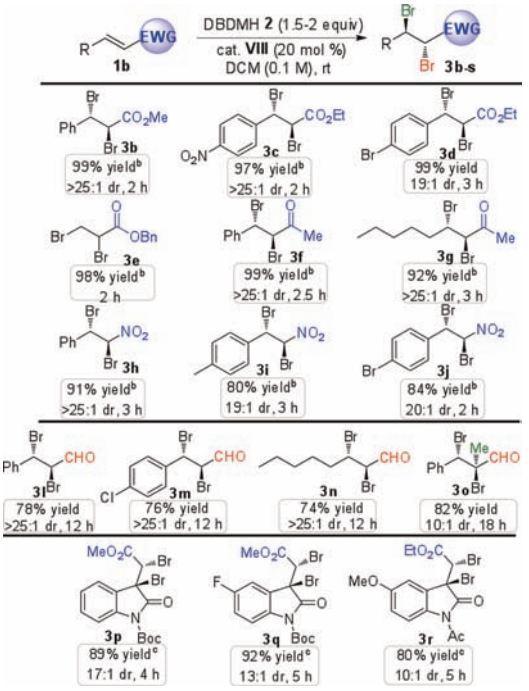
[a] Reactions were carried out using **1** (0.2 mmol) and DBDMH **2** (0.4 mmol) in solvent (2 mL) with 20 mol % of catalyst **VIII** at rt. [b] Isolated yields. [c] Determined by crude ^{1}H NMR.

any catalyst, no reaction occurs and that the use of other common bromonium sources, such as NBS, with catalyst **VIII** gave the dibrominated product with less than 20% conversion. Since we observed increased reactivity with thiourea catalysts containing a tertiary amine, we evaluated how an external amine affected the reaction. When combined with a thiourea catalyst, Et_3N significantly enhanced the reaction rate. Dibromination of chalcone **1** with catalyst **X** in the presence of 20 mol % of Et_3N was complete in only 30 min vs the 10 h needed without the additive (entry 11). However, Et_3N did not influence the diastereoselectivity. Optimal results were obtained in the reaction performed in presence of catalyst **II** and Et_3N; total conversion and 94% yield were obtained in just 30 min with excellent diastereoselectivity (entry 12). We then studied the generality of the dibromination reactions using the bifunctional catalyst **VIII** and the combination of thiourea **II** and Et_3N. Both systems yielded the desired products in reactions with nonfunctionalized olefins, but better results were obtained with catalyst **VIII** when other functional groups were present. Therefore, we further optimized conditions for use of catalyst **VIII**.

We first evaluated the solvent effect. The dibrominated product **3** was obtained in high yields and dr with short reaction times with the solvents tested except acetone (Table 2). In this case, hydroxylic attack at the reactive bromonium intermediate presumably occurred more rapidly than the bromine attack, and *trans*-bromo hydroxylated compound **4** was isolated as the major product. Long reaction times were necessary for completion of the reaction in solvents with low polarity indices such as toluene (Table 2, entry 1). More polar solvents as MeCN (entry 7) required shorter reaction times. Of those tested, halogenated solvents DCM and $CHCl_3$ proved to be the best with respect to catalytic activity and selectivity, but toluene, 1,4-dioxane, EtOAc, and water/DCM were acceptable. Nonhalogenated solvents render that methodology more environmentally benign.

Encouraged by these results, we evaluated the efficacy of dibromination of different functionalized olefins containing

Scheme 1. Generality of the Dibromination Reaction[a,b,c]

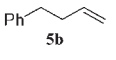
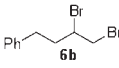
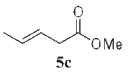
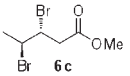
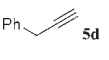
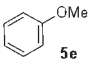
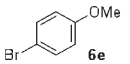


[a] Unless otherwise specified, all reactions were carried out using olefins **1b**–**r** (1 equiv) and DBDMH **2** (2 equiv) in DCM (0.1 M) with 20 mol % of catalyst **VIII** at rt. [b] 1.5 equiv. [c] Et_2O was used as solvent.

electron-withdrawing groups as shown in Scheme 1. The use of 1.5 equiv of DBHDM and 20 mol % of thiourea catalyst **VIII** in DCM at rt resulted in compete reaction of the starting material. Under these conditions, reaction of terminal and substituted deactivated olefins containing esters, ketones, and nitro functionalities with aryl and alkyl substituents (**1b**–**j**) provided dibrominated products **3b**–**j** with excellent yields and diastereoselectivities (Scheme 1).

The α,β-unsaturated aldehydes are interesting substrates. The dibromination of *trans*-cinnamaldehyde occurred to form **3l** with good yield and excellent diastereselectivity after 12 h of stirring at rt using 2 equiv of DBDMH (Scheme 1). α,β-Unsaturated aldehydes with chlorine on the aromatic moiety, alkyl substituents, or α-substituted enals were also acceptable reactants, and the corresponding dibrominated aldehydes **3m**–**o** were obtained in good yields. Finally, we evaluated different methyleneindolinones. Oxindole motifs are widely present in natural products and bioactive molecules;[15] in particular oxindole compounds bearing a quaternary stereogenic center at the 3-position are extremely useful. The dibrominated products **3p**–**3r** containing different substitutions in the aromatic moiety or different N-protecting groups were formed in high yields, although without total stereocontrol. For these compounds, a slight improvement in the diasteroselection was observed when Et_2O was used as solvent; dr's of up to 17:1 were obtained (Scheme 1). The *anti* stereochemistry of compound **3p** was established by X-ray analysis (see Supporting Information).

Table 3. Dibromination of Organic Substrates[a]

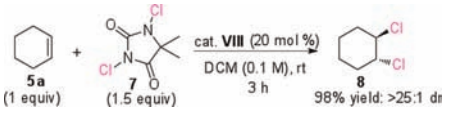
entry	substrate	product	time	yield[b]	dr[c]
1	 5a	 6a	4 h	92%	>25:1
2[d]	 5b	 6b	4 h	62%	-
3[d]	 5c	 6c	1.5 h	55%	20:1
4[e]	 5d	 6d	1.5 h	85%	>25:1
5	 5e	 6e	2 h	95%	-

[a] Unless otherwise specified, all reactions were carried out using compounds **5a**–**e** (1 equiv) and DBDMH **2** (1.5 equiv) in DCM (0.1 M) with 20 mol % of catalyst **VIII** at rt. [b] Isolated yields. [c] Determined by crude ^{1}H NMR [d] Reaction carried out using 2 equiv of DBDMH. [e] Reaction carried out using 1 equiv of DBDMH.

Various alkenes, compounds with acetylenic functionality, and aromatic compounds were successfully subjected to the bromination conditions as shown in Table 3.

With these results in hand, the applicability of this organocatalyzed methodology to dichlorination processes[9] was evaluated. The commercially available analogue 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) **7** was used as a chlorine source. Treatment of cyclohexene **5a** with 1.5 equiv of DCDMH in DCM at rt gave rise to the desired dichlorinated product in excellent yield and diastereoselectivity (Scheme 2).

Scheme 2. Dichlorination Reaction



Since the chloronium anion intermediates that give rise to the dichlorinated compounds show higher configurational stability than their bromonium analogues,[16] this dichlorination process should be evaluated in asymmetric dihalogenations.

Although the mechanism of this reaction has not been completely elucidated, we believe that the thiourea and amine groups of the catalyst **VIII** activate the DBDMH and allow fast *in situ* generation of bromine which subsequently reacts with the unsaturated compounds. The colorless solution of olefin and DBDMH in DCM turns dark red when catalyst **VIII** is added, suggesting that Br_2 is generated. The solution loses color as the reaction proceeds. Sulfur containing compounds show a complex free-radical chemistry, and radical reactions, where the sulfur atom of different thioureas is involved, are known.[17] Control experiments showed no reaction of **1p** using the usual conditions but in the absence of ambient light or in the presence of TEMPO (Scheme 3), which could act as a radical inhibitor. We propose that the sulfur atom of the thiourea catalyst is involved in a radical reaction and might generate the bromide anion required to react with the DBDMH and form the Br_2 observed in the reaction media.[18] Additional interactions between the *in situ* formed Br_2, substrate, and catalyst may also occur.

Scheme 3. Control Experiments in Support of Mechanism

[a] Reaction carried out in an amber vial covered by aluminum foil in the dark for 3 h.

In summary, the organocatalytic and selective character of the reported process and the nonhazardous reaction components, mild conditions used, and short times required for completion render this dihalogenation method an extremely practical and safe method for the bromination and chlorination of unsaturated compounds. A broad substrate scope was demonstrated: both acyclic and cyclic alkenes, alkynes, and activated aromatic rings are good substrates for the halogenation reaction catalyzed by **VIII** in the presence of DBDMH. This methodology holds promise for the synthesis of enantioenriched dihalogenated products starting from achiral unsaturated compounds. Efforts to achieve enantioselectivity are underway in our laboratory.

Acknowledgment. Research support from the Skaggs Institute for Chemical Biology is gratefully acknowledged. We also thank Dr. A. L. Rheingold and Dr. C. E. Moore (UC San Diego) for X-ray crystallographic analysis. G.H.-T. also thanks Universidad Autónoma de Madrid for financial support.

Supporting Information Available. Experimental procedures, characterization of compounds, and X-ray data (CIF file) of **3p**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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