JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Chiral Helical Oligotriazoles: New Class of Anion-Binding Catalysts for the Asymmetric Dearomatization of Electron-Deficient *N*-Heteroarenes

Mercedes Zurro,[†,‡] Sören Asmus,[†,‡] Stephan Beckendorf,[‡] Christian Mück-Lichtenfeld,[‡] and Olga García Mancheño*[,†,‡,§]

[†]Institute of Organic Chemistry, University of Münster, 48149 Münster, Germany

[‡]Institute for Organic Chemistry, University of Regensburg, 93053 Regensburg, Germany

[§]Straubing Center of Science, 94315 Straubing, Germany

Supporting Information

ABSTRACT: Helical chirality and selective anion-binding processes are key strategies used in nature to promote highly enantioselective chemical reactions. Although enormous efforts have been made to develop simple helical chiral systems and thus open new possibilities in asymmetric catalysis and synthesis, the efficient use of synthetic oligo- and polymeric helical chiral catalysts is still very challenging and rather unusual. In this work, structural unique chiral oligotriazoles have been developed as C−H bond-based anion-binding catalysts for the asymmetric dearomatization of *N*-heteroarenes. These rotational flexible catalysts adopt a reinforced chiral helical conformation upon binding to a chloride anion, allowing high levels of chirality transfer via a close chiral anion-pair complex with a preformed ionic substrate. This methodology offers a straightforward and potent entry to the synthesis of chiral (bioactive)heterocycles with added synthetic value from simple and abundant heteroarenes.

Anion-binding catalysis is becoming a powerful tool in hydrogen-bond-donor catalysis and organic synthesis.[1] Besides the more traditional H-bonding catalytic approaches that imply the activation of neutral electrophiles[2] or the use of ion-pairing initiated by protonation with a Brønsted acid,[3] anion-binding catalysis is based on the activation of an ionic electrophile by binding the catalyst to its counteranion (Figure 1). A close ion-pair between the substrate and the catalyst−anion complex is formed, facilitating the attack of the nucleophile. Moreover, when a chiral catalyst is used, the catalyst−anion complex becomes chiral, and a chirality transfer to the final product can be achieved.

To date, (thio)ureas, based on strong polarized N−H bonds as H-bond donors, have demonstrated a distinctive reactivity.[1,4] However, in the past few years, catalyst structures such as thiophosphoramides (based on N−H bonds),[5] siladienols (based on O−H bonds),[6] or the bistriazoles recently introduced by our research group[7] (based on the cooperative action of "low-polarized" C−H bonds as weak H-donors[8]) have also shown the ability to promote reactions through anion-binding catalysis. However, to further innovate in the area of anion-binding catalysis and to attain previously inaccessible enantioselective transformations, the development of original chiral catalyst-motifs is highly desirable.

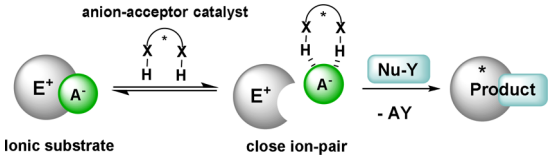


Figure 1. Anion-binding catalysis approach.

Encouraged by the great synthetic potential of enantioselective anion-binding catalysis, we pursued the development of a conceptually novel family of chiral helical organocatalysts (Figure 2). The efficient transfer of chirality from oligo- and polymeric helical catalysts is rather unusual;[9] the design of simple dynamic helical chiral systems that can easily be tuned and controlled would offer new entries in asymmetric catalysis.[10]

Based on our first promising results using bistriazole-based systems (**BisTri**) as selective chloride-anion-binding catalysts[7] and inspired by known helicenes derived from prolonged condensed aromatic systems that cannot adopt a planar conformation,[11] extended structures with four triazole units (**TetraTri**) have been designed.[12] Flexibility would still be present in these systems since the (hetero)aromatic subunits would be linked by σ-bonds. Having such highly flexible structures, which in normal conditions will present in equilibrium both linear and helical conformations, a reinforced defined helical system can be envisioned upon complexation to a chloride anion.[13] Thus, a favored defined chiral helical triazole−chloride anion complex might be formed. This special feature and concept can be then employed for chasing challenging asymmetric transformations using anion-binding catalysis.

In this regard, we became highly interested in the enantioselective dearomatization of simple and abundant heteroaromatic compounds,[14] which constitutes an elegant and straightforward approach to generate synthetically valuable *N*-heterocycles possessing new stereocenters. *N*-Heterocycles are widely occurring key structural units in a variety of natural and synthetic bioactive molecules.[15] Consequently, their synthetic

Received: August 3, 2014
Published: September 11, 2014

   dx.doi.org/10.1021/ja507940k | *J. Am. Chem. Soc.* 2014, 136, 13999−14002

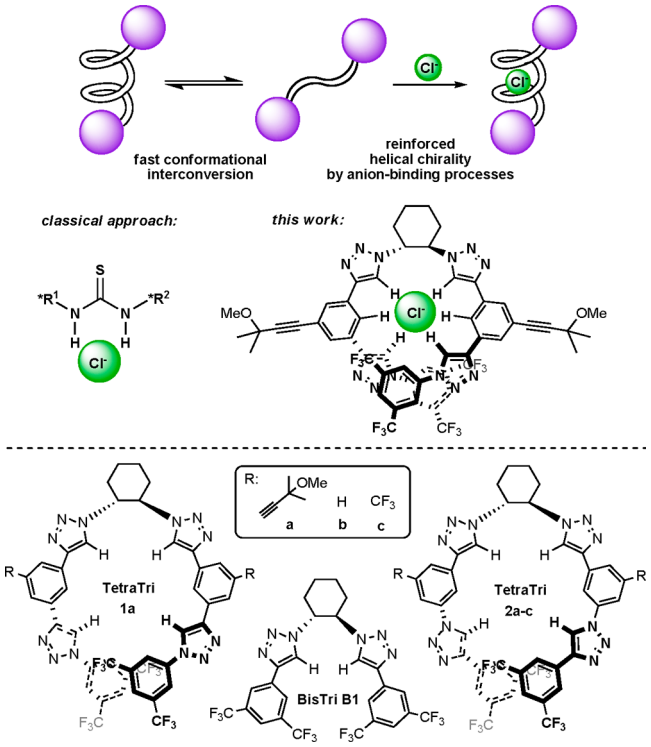


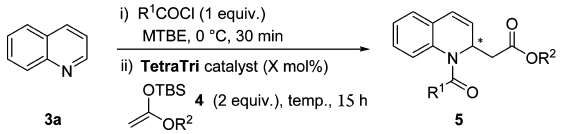
Figure 2. Chiral helical reinforced conformation for asymmetric anion-binding catalysis and designed triazole-based catalysts.

modification is of great importance in both academia and industry. In recent years, several dearomatization reactions have been developed; the most common strategy implies first the activation of the heteroaromatic ring by *N*-acylation, followed by nucleophilic attack.[14] However, despite the high potential of employing the dearomatization technique, catalytic asymmetric processes are still very challenging and rare.[14] Thus, only limited methods implying organocatalysis for the efficient enantioselective nucleophilic dearomatization of electron-deficient *N*-heteroarenes have been reported.[6,16]

Here we described a new kind of C−H bond-based helical triazole anion-binding catalyst for the enantioselective dearomatization of quinolines by C2-selective nucleophilic addition of silyl ketene acetals as enolate equivalents.[17]

Initially, a small family of chiral triazole-based catalysts were synthesized from appropriate bromo-substituted benzenes as simple starting materials using iterative Sonogashira couplings, terminal alkyne deprotection, and Cu-catalyzed azide−alkyne 1,3-cycloadditions (see Supporting Information (SI) for more details). Chiral 1,2-diamines were used as backbone to preorientate and later on guide the formation of one of the two possible chiral helices upon binding to the chloride anion. With these anion-binding catalysts **TetraTri 1** and **2** in hand, we explored the asymmetric dearomatization of quinolines (Table 1). *N*-Acyl Mannich addition with silyl ketene acetals was selected as a suitable testing transformation for H-bond donor activation, based on a prior related thiourea-based catalyzed reaction with isoquinolines reported by Jacobsen et al.[16a] We started our screening with simple and readily available quinoline (**3a**) as a model substrate, 2,2,2-trichloroethyl chloroformate (TrocCl, $R^1 = OCH_2CCl_3$) as acylating agent, and isopropyl TBS-ketene acetal **4a** in the presence of 10 mol% of the **TetraTri** catalyst. The reaction was carried out in methyl *tert*-butyl ether (MTBE), initially at −78 °C, and allowed to slowly reach room

Table 1. Optimization of Catalyst, Acylating Agent, and Nucleophile[a]



entry	R^1	R^2	catalyst (mol%)	temp. (°C)	Prod.	yield[b] (%)	e.r.[c]
1	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**1a** (10)	-78 – rt	**5a**	76	96:4
2	OCH_2CCl_3	*i*Pr	(*S*,*S*)-**1a** (10)	-78 – rt	**5a**	70	4:96
3	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**2a** (10)	-78 – rt	**5a**	80	95:5
4	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**2b** (10)	-78 – rt	**5a**	82	81:19
5	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**2c** (10)	-78 – rt	**5a**	61	84:16
6	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**B1** (10)	-78 – rt	**5a**	91	41:59
7	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**1a** (10)	-78	**5a**	51	95:5
8	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**1a** (10)	-30	**5a**	87	91:9
9	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**1a** (10)	rt	**5a**	76	70:30
10	OCH_2CCl_3	*t*Bu	(*R*,*R*)-**1a** (10)	-78 – rt	**5b**	58	98:2
11	OCH_2CCl_3	Me	(*R*,*R*)-**1a** (10)	-78 – rt	**5c**	56	64:36
12	OEt	*i*Pr	(*R*,*R*)-**1a** (10)	-78 – rt	**6**	37	52:48
13	OBn	*i*Pr	(*R*,*R*)-**1a** (10)	-78 – rt	**7**	58	58:42
14	Me	*i*Pr	(*R*,*R*)-**1a** (10)	-78 – rt	**8**	--	--
15	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**1a** (5)	-78 – rt	**5a**	64	95:5
16	OCH_2CCl_3	*i*Pr	(*R*,*R*)-**1a** (2.5)	-78 – rt	**5a**	44	95:5
17	OCH_2CCl_3	*i*Pr	--	-78 – rt	**5a**	45	50:50

[a]Conditions: (i) **3a** (1.0 equiv) and R^1COCl (1.0 equiv) in MTBE at 0 °C, 30 min; (ii) at the corresponding temperature, catalyst (2.5−10 mol%) and **4** (2 equiv) were added and stirred for 15 h. [b]Isolated yield. [c]Values for er were determined by chiral HPLC.

temperature (rt) overnight. The first catalyst tested, (*R*,*R*)-**1a**, already possessing an alkynyl substituent, provided a high enantioselectivity (entry 1, 96:4 er). Use of the enantiomer (*S*,*S*)-**1a** or the regioisomer (*R*,*R*)-**2a** with the same alkynyl substitution pattern provided similar levels of enantioinduction in forming the opposite enantiomer and product **5a**, respectively (entries 2,3). In contrast, the catalysts with no substituent **2b** or CF_3 groups **2c** showed low chirality transfer efficiencies (entries 4,5). Reaction in the presence of **BisTri** catalyst **B1**, which cannot present helical chirality upon binding to the chloride anion, was also carried out (entry 6). **5c** was then obtained in excellent yield but with a very poor enantioselectivity (41:59 er), suggesting that the central chirality of the bis-diamine unit is not sufficient for an efficient asymmetric induction. Subsequently, **1a** was further employed as the most efficient catalyst.

Despite the exceptional enantioselectivities obtained by the experimentally simplified initial setup at −78 °C followed by a gradual increase of the temperature, reactions under constant temperatures and controlled gradients were then studied in order gain a better understanding of the reaction requirements. When the reaction was carried out at −78 °C for 15 h, comparable enantioselectivity (95:5 er) and a lower yield (51%) were

dx.doi.org/10.1021/ja507940k | *J. Am. Chem. Soc.* 2014, 136, 13999−14002

obtained (entry 7). As expected, higher reaction temperatures led to a notable drop in the er (entries 8,9). These results show the crucial influence of the initial reaction temperature on the transfer of chirality from the catalyst to the product.

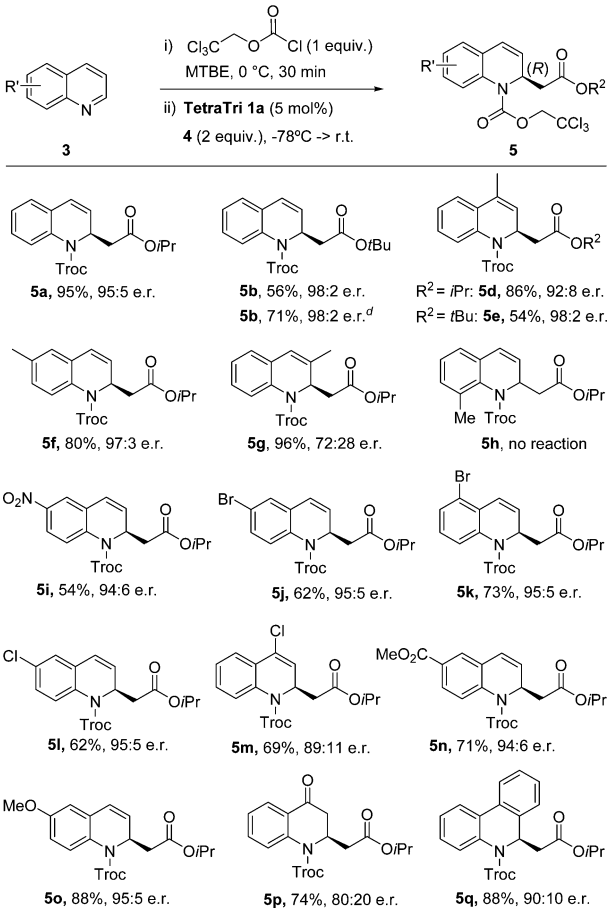
It was next found that the reaction depended strongly on the nature of the nucleophile and acylating agent employed (entries 10−14). Regarding the nucleophiles **4**, a clear trend was observed: the bulkier the silyl ketene acetal (*t*Bu > *i*Pr > Me) was, the higher was the enantioselectivity. Thus, the *t*Bu-substituted reagent afforded the best enantioselectivity (98:2 er) in a moderate yield (58%), while the *i*Pr derivative provided both a high enantioselectivity (96:4 er) and a good yield (76%). Alternately, only chloroformates showed reactivity and selectivity. In particular, TrocCl led to the higher enantioselectivity, while the other tested acylating agents induced poor chiral inductions.[18]

Finally, the catalytic loading could also be reduced to 5 and 2.5 mol% without detriment on the enantioselectivity, but the conversion decreased gradually (entries 15,16). As a compromise, a catalytic loading of 5 mol% was chosen for the further substrate scope studies (Table 2). Under the optimized conditions, various commercially available quinolines with different substitution patterns were explored. Though the reaction with the *tert*-butyl ketene acetal provided generally the products **5** in higher er (**5b**, **5c**), to attain as well high conversions the study was completed with the *i*Pr derivative as nucleophile. Initial studies with methylquinolines already showed that substitutions at nearly all positions at the quinoline core were well tolerated, and **5d−f** were obtained with high er (up to 98:2 er). However, substitution at the C3 position led to a significant decrease on the er (**5g**, 72:28 er), and the presence of a substituent at the C8 position (**3h**) inhibited completely the reaction. These results could be explained in terms of steric hindrance. Thus, a substituent in the C8 position will prevent the bulky Troc group to rotate out from the active site, impeding the attack of the nucleophile. On the other hand, substituents attached to the C3 position might also hamper the approach of the nucleophile to the C2 position, causing a deficient differentiation of both faces of the quinoline derivative. Furthermore, both the electron-poor and the electron-rich substituted quinolines provided the dearomatized products **5i−q** in similar good yields and excellent enantioselectivities (typically 95:5 er). Interestingly, 4-methoxyquinoline provided the 2-substituted chiral 4-quinolone **5p** in a moderate 80:20 er.

The absolute configuration of the major enantiomer of **5b** (98:2 er) was determined as the (*R*) by comparison between the measured and DFT-simulated CD spectra and by derivatization of **5a** (93:7 er) to the NH-free *β*-amino methyl ester[19] (see SI). Assuming the same behavior of the catalytic system, the configuration of the other hydroquinoline products **5** was also assigned as (*R*) by analogy.

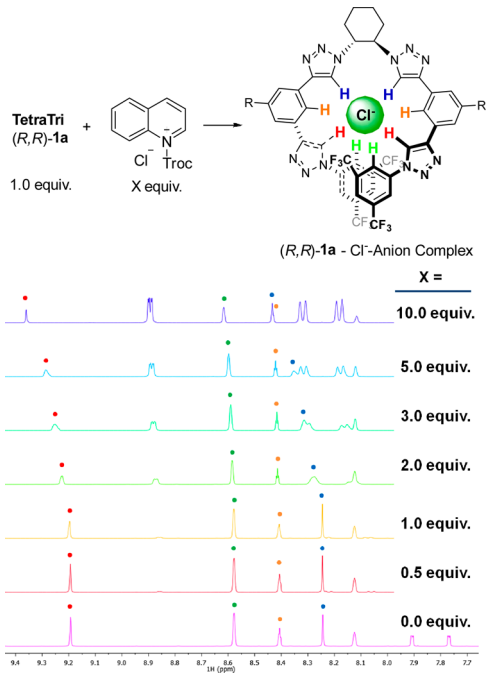
To get a better understanding on the activity and behavior of the **TetraTri** catalysts, a ^{1}H NMR titration of (*R*,*R*)-**1a** with the preformed quinolinium chloride **6** as the active ionic substrate was carried out. As it can be seen in Scheme 1, the proton signals of the C−H bonds of the triazoles are clearly shifted downfield after the addition of at least 1 equiv of the preformed ionic substrate **6**. For example, addition of 10 equiv of **6** translated to the same chemical shift of ∼1.5 ppm for the H atoms of the both **BisTri** subunits (blue and red). There are also slight changes in the chemical shifts of other aromatic H atoms.[20] All this suggests

Table 2. Scope of the Reaction[a,b,c]



[a]Conditions: (i) **3** (1.0 equiv) and TrocCl (1.0 equiv) in MTBE at 0 °C, 30 min; then −78 °C; (ii) catalyst **1a** (5 mol%) and **4** (2 equiv) were added, and the temperature was slowly allowed to reach rt (20−24 h). [b]Isolated yields. [c]Values for er were determined by chiral HPLC. [d]5 mmol scale reaction (2.5 mol% of **1a**, 4 days).

Scheme 1. ^{1}H NMR Titration of 1a with Quinolinium Salt 6



dx.doi.org/10.1021/ja507940k | J. Am. Chem. Soc. 2014, 136, 13999−14002

a cooperative H-bond to the chloride anion, which is accommodated inside the helical cavity of the catalyst.

Circular dichroism (CD) titration of the catalyst (*R*,*R*)-**1a** (0.133 mM solution in THF) with Bu_4NCl was next carried out. The characteristic chirality of the helical backbone allows observing conformational changes in helically folding flexible oligomers by CD spectroscopy. Binding of a guest, in our case a chloride anion, might provoke the formation of an excess of one of the helical forms. This type of conformational change will be then associated with an induced CD effect. The titration curve displayed in Figure 3 shows the envisioned reinforcement or

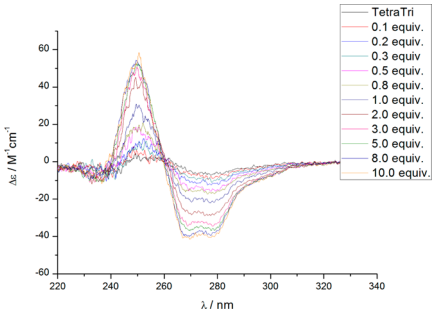


Figure 3. CD tritation of **TetraTri 1a** with Bu_4NCl in THF.

amplification of the helical structure of the catalyst in solution by binding to a chloride anion. Thus, addition of Cl^-, translated into a notable increase of the characteristic absorption bands at 250 and 265−280 nm in the positive and negative regions of the UV spectrum, respectively.

In conclusion, novel helical chiral oligotriazoles have been developed as anion-binding catalysts for the asymmetric dearomatization of quinolines. These catalysts transfer the chirality effectively to the dearomatized products via formation of a close chiral anion-pair complex with a preformed *N*-acylquinolinium ionic substrate. Cooperative binding of the catalyst's triazole and aromatic C−H bonds in its cavity to the chloride anion, and the reinforced catalyst helical structure upon this coordination, were confirmed by ^1H NMR and CD titration experiments, respectively. The unique features of the presented triazole organocatalysts might also unveil further interesting applications in asymmetric anion-binding catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

olga.garcia-mancheno@ur.de

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Deutscher Akademischer Austauschdienst are acknowledged for generous support.

■ REFERENCES

(1) (a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (b) Beckendorf, S.; Asmus, S.; García Mancheño, O. *ChemCatChem* **2012**, *4*, 926. (c) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534. (d) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. Seidel, D. *Synlett* **2014**, *25*, 783.

(2) (a) Pihko, P. M. *Hydrogen Bonding in Organic Chemistry*; Wiley-VCH: Weinheim, 2009. (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (c) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (f) Jacobsen, E. N.; Knowles, R. R. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678.

(3) (a) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (b) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603 and refs therein.

(4) Pioneering work: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.

(5) Borovika, A.; Tang, P.-I.; Klapman, S.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 13424.

(6) Schafer, A. G.; Wieting, J. M.; Fisher, T. J.; Mattson, A. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 11321.

(7) (a) Beckendorf, S.; Asmus, S.; Mück-Lichtenfeld, C.; García Mancheño, O. *Chem.—Eur. J.* **2013**, *19*, 1581. (b) Asmus, S.; Beckendorf, S.; Zurro, M.; Mück-Lichtenfeld, C.; García Mancheño, O. *Chem. Asian. J.* **2014**, *9*, 2178.

(8) Selected examples on triazole and triazolium salts C−H-based H-donors: (a) Li, Y.; Flood, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2649. (b) Meudtner, R. M.; Hecht, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4926. (c) Juwarker, H.; Lenhardt, J. M.; Pham, D. M.; Craig, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 3740. (d) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* **2011**, *133*, 1307.

(9) For example: (a) Yamamoto, T.; Suginome, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 539. (b) Reggelin, M.; Schultz, M.; Holbach, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1614.

(10) Selected examples of helical chiral organocatalysts: (a) Takenaka, N.; Chen, J.; Captain, B.; Sarangthem, R. S.; Chandrakumar, A. *J. Am. Chem. Soc.* **2010**, *132*, 4536. (b) Chen, J.; Captain, B.; Takenaka, N. *Org. Lett.* **2011**, *13*, 1654. (c) Crittall, M. R.; Rzepa, H. S.; Carbery, D. R. *Org. Lett.* **2011**, *13*, 1250. (d) Mortezaei, S.; Catarineu, N. R.; Canary, J. W. *J. Am. Chem. Soc.* **2012**, *134*, 8054. (e) Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2013**, *135*, 10598. (f) Wang, J.; Feringa, B. L. *Science* **2011**, *331*, 1429.

(11) Shen, Y.; Chen, C.-F. *Chem. Rev.* **2012**, *112*, 1463. Gingras, M.; Félix, G.; Peresuttiab, R. *Chem. Soc. Rev.* **2013**, *42*, 1007.

(12) Recent review on triazole chemistry: (a) Schulze, B.; Schubert, U. S. *Chem. Soc. Rev.* **2014**, *53*, 2522. Application as catalysts: (b) Beckendorf, S.; García Mancheño, O. *Synthesis* **2012**, *44*, 2162. (c) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14044.

(13) Induction of helical chirality upon anion-binding: (a) Suk, J.; Naidu, V. R.; Liu, X.; Lah, M. S.; Jeong, K.-S. *J. Am. Chem. Soc.* **2011**, *133*, 13938. (b) Suk, J.; Kim, D.; Jeong, K.-S. *Org. Lett.* **2012**, *14*, 5018. See also refs 8a,b.

(14) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662 and refs therein.

(15) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 5th ed.; Wiley: New York, 2010.

(16) For example: (a) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700. (b) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686. (c) Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058.

(17) Lead work: (a) Akiba, K.; Kobayashi, T.; Yamamoto, Y. *Heterocycles* **1984**, *22*, 1519. Itoh, T.; Miyazaki, M.; Nagata, K.; Ohsawa, A. *Heterocycles* **1997**, *46*, 83. First asymmetric example: (b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327.

(18) See SI for Br^- and BF_4^- counteranion effects.

(19) Katayama, S.; Ae, N.; Nagata, R. *Tetrahedron: Asymmetry* **1998**, *9*, 4295.

(20) Zhang, Z.; Lippert, K. M.; Hausmann, H.; Kotke, M.; Schreiner, P. R. *J. Org. Chem.* **2011**, *76*, 9764.