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Silver-Catalyzed Asymmetric Desymmetrization of Cyclopentenediones via [3 + 2] Cycloaddition with α-Substituted Isocyanoacetates

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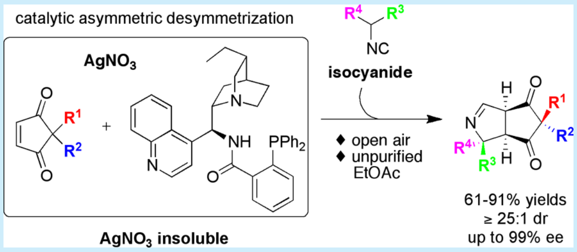
Supporting Information

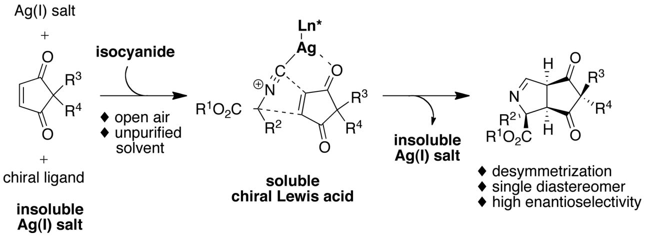
ABSTRACT: A highly selective and practical asymmetric Ag(I) catalyst system has been developed for the [3 + 2] cycloaddition reactions between isocyanoacetates and cyclopentenediones. The current Ag(I) catalyst system tolerates moisture and air and readily utilizes class III solvents such as EtOAc and acetone. The development of *on demand* generation of an active chiral catalyst in the presence of isocyanides paves a way to the efficient asymmetric preparation of bicyclic pyrrolidines with four stereogenic centers, including two quaternary centers in 80−97% ee.



Lewis acids occupy a prominent position in organic synthesis, as they enable highly selective organic transformations to be performed under mild reaction conditions. The use of transition-metal-based Lewis acid catalysts has broadened the substrate scope beyond typical Lewis basic functional groups to less Lewis basic chemical moieties thanks to their unique redox chemistry.[1] Among other transition metals, silver catalysts dexterously interact with π donors as well as σ donors, where the silver cation character can be tuned for the in situ generation of active silver catalysts with better reactivity and selectivity.[2] The pioneering work by Hayashi and Ito on isocyano aldol reactions in 1990 laid the foundation for the chiral ferrocenylphosphine−Ag(I) complexes as mild Lewis acid catalysts.[3] The subsequent development of the BINAP−Ag(I) catalyst system by Yamamoto and Yanagisawa significantly expanded the generality of the chiral silver Lewis acid catalysts to asymmetric aldol and allylation reactions with excellent reactivity and selectivity.[4] A new turn in asymmetric Ag(I) catalysts was marked in 2003 when Hoveyda and Snapper introduced amino acid-derived phosphine−Ag(I) catalysts.[5] These catalysts possess increased stability toward moisture and air and deliver the highly efficient and selective preparation of optical isomers. While the recent development of enantioselective silver-catalyzed reactions amply demonstrates their synthetic potential in C−C bond-forming reactions,[6] the discovery of air- and moisture-tolerant chiral Lewis acid catalysts is in critical need. Defying the intrinsic sensitivity of Lewis acids to air and moisture can lead to operationally simple experimental procedures for the asymmetric silver catalysts without the need for special care and techniques. Herein we report the development of asymmetric $AgNO_3$-catalyzed [3 + 2] cycloaddition reactions of isocyanoacetates with cyclopentenediones via desymmetrization in the presence of a cinchona-derived aminophosphine ligand. The current asymmetric silver catalyst system boasts the following practical aspects: air and moisture tolerance, short reaction time, and catalyst loading as low as 2 mol % to give products with four chiral centers in excellent yields and stereoselectivities.

The idea of practical silver catalysis was explored in the asymmetric transformation of isocyanoacetates on the basis of the strong coordination ability of isocyanides to silver ions, where the development of metal-catalyzed asymmetric functionalizations of isocyanides remains a significant challenge.[7] To drastically increase the molecular complexity, we chose the intermolecular [3 + 2] cycloaddition reaction of isocyanoacetates with prochiral cyclopentenediones (Scheme 1). While catalytic asymmetric desymmetrization reactions[8] of cyclopentenediones have been explored in asymmetric reductions,[9] conjugate additions,[10] formal C(sp^2)−H alkenylation,[11] the oxidative Heck reaction,[12] and azomethine [3 + 2] cycloaddition reactions,[13] to the best of our knowledge the use

Scheme 1. Catalytic Asymmetric Ag(I)-Catalyzed [3 + 2] Cycloaddition Reaction via Desymmetrization



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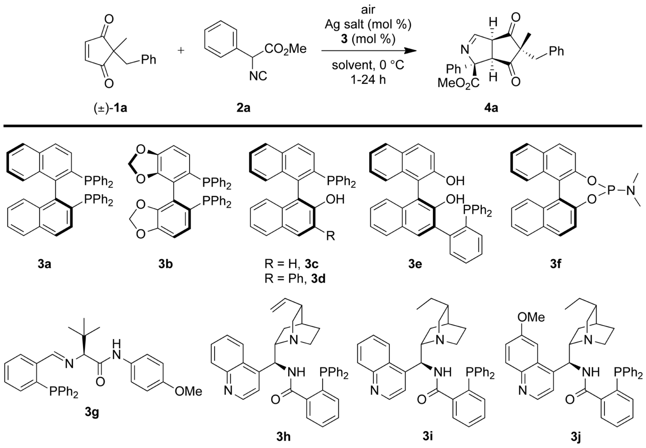
of isocyanides in the asymmetric transformation of cyclopentenediones has not been examined.

Among various silver salts, we chose the least soluble Ag(I) source in organic solvents, such as $AgNO_3$, for the reaction optimization studies, given the fact that isocyanides can dissociate such insoluble silver salts to the organic solution.[14] Thus, a mixture of cyclopentenedione **1a**, silver salt, and chiral ligand **3** in unpurified EtOAc, a class III solvent,[15] was prepared under open air conditions. The reaction mixture clearly showed the insoluble $AgNO_3$ as clear crystals. Initially, we screened phosphine ligands **3a**–**j** to identify a suitable asymmetric scaffold for $AgNO_3$ (Table 1). Upon the addition of *α*-phenyl isocyanoacetate **2a** to the reaction mixture, dissolution of the solid $AgNO_3$ was observed, but no reaction was observed at 0 °C for 12 h. The use of a base such as Et_3N was necessary for binaphthyl-based phosphine ligands **3a**–**f** to effect the formation of a single diastereomeric product, **4a** (entries 1–6). While low reactivity and enantioselectivity were observed for chiral ligands such as BINAP (**3a**) and SEGPHOS (**3b**), the use of binaphthyl monophosphine ligand **3c** slightly improved the reactivity to 59% with 51% ee (entry 3). Other BINOL platform ligands, monodentate phosphine ligand **3e** and phosphoramidite **3f**, provided the desired product **4a** with low enantioselectivities (entries 5 and 6). The Hoveyda–Snapper catalyst **3g**[5] prompted the formation of **4a** in 86% conversion with 54% ee (entry 7), but the Dixon's cinchona-alkaloid-based phosphine ligands **3h**–**j**[16] drastically improved the conversions and enantioselectivities to >90% (entries 8–10). The use of other silver salts also provided comparable results (entries 11–14), demonstrating the robustness of the current catalyst system. Solvent screening including another class III solvent, acetone, revealed that the reaction proceeded smoothly without other side reactions,[17] offering the potential use of the catalyst system in industry (entries 15–17). Our control experiments also showed that the catalyst system displays (1) water tolerance (entry 18), (2) a short reaction time of 15 min at 23 °C (entry 19), (3) a higher selectivity of 95% ee at −40 °C (entry 20), (4) irrelevance of the $AgNO_3$ loading (entry 21), (5) a lower catalyst loading (entry 22), and (6) the importance of Ag(I) salt (entry 23).

Table 1. Silver-Catalyzed [3 + 2] Cycloaddition Reaction via Desymmetrization[a]



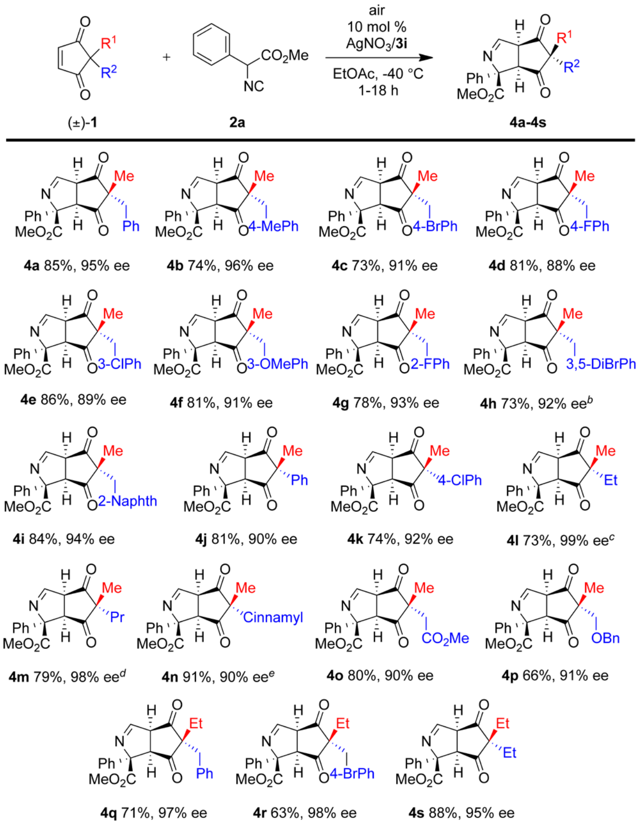
entry	Ag (mol %)	ligand (mol %)	solvent	conv (%)[b]	ee (%)[c]
1[d]	$AgNO_3$ (10)	**3a** (10)	EtOAc	24	2
2[d]	$AgNO_3$ (10)	**3b** (10)	EtOAc	41	9
3[d]	$AgNO_3$ (10)	**3c** (10)	EtOAc	59	51
4[d]	$AgNO_3$ (10)	**3d** (10)	EtOAc	60	4
5[d]	$AgNO_3$ (10)	**3e** (10)	EtOAc	53	18
6[d]	$AgNO_3$ (10)	**3f** (10)	EtOAc	74	3
7	$AgNO_3$ (10)	**3g** (10)	EtOAc	86	54
8	$AgNO_3$ (10)	**3h** (10)	EtOAc	99	88
9	$AgNO_3$ (10)	**3i** (10)	EtOAc	96	93
10	$AgNO_3$ (10)	**3j** (10)	EtOAc	94	89
11	AgF (10)	**3i** (10)	EtOAc	95	91
12	AgOAc (10)	**3i** (10)	EtOAc	98	87
13	$AgClO_4$ (10)	**3i** (10)	EtOAc	96	93
14	Ag_2O (10)	**3i** (10)	EtOAc	99	91
15	$AgNO_3$ (10)	**3i** (10)	$PhCH_3$	98	87
16	$AgNO_3$ (10)	**3i** (10)	EtOH	98	36
17	$AgNO_3$ (10)	**3i** (10)	acetone	99 (86)	91
18[e]	$AgNO_3$ (10)	**3i** (10)	EtOAc	99	92
19[f]	$AgNO_3$ (10)	**3i** (10)	EtOAc	99	81
20[g]	$AgNO_3$ (10)	**3i** (10)	EtOAc	99 (85)	95
21[g]	$AgNO_3$ (100)	**3i** (10)	EtOAc	99	93
22[g]	$AgNO_3$ (5)	**3i** (5)	EtOAc	99	92
23[h]	–	**3i** (10)	EtOAc	0	0

[a] Reaction conditions: **1a** (0.12 mmol) and **2a** (0.10 mmol) in the solvent (0.10 M) under air. [b] Determined by ^1H NMR analysis. Values in parentheses are isolated yields. [c] Determined by HPLC using a chiral column. [d] Et_3N (10 mol %) was used. [e] EtOAc saturated with water. [f] Reaction at 23 °C. [g] Reaction at −40 °C. [h] No Ag(I) salt.

With the robust $AgNO_3$-catalyzed asymmetric system in place, the scope of cyclopentenediones was investigated, as shown in Scheme 2. The catalyst system was applicable to an extensive array of cyclopentenediones with different electronic and steric characters. Thus, methylcyclopentenediones with a variety of benzyl substituents provided products **4a**–**j** with excellent diastereo- and enantioselectivities, where the catalyst system displayed high desymmetrization capability. The employment of methylcyclopentenediones with phenyl derivatives was also successful, and the absolute configuration was established by X-ray crystallographic analysis of **4k**. The cyclopentenediones with two alkyl substituents led to mixtures of diastereomers **4l** and **4m**, but the crude mixtures could be further purified by recrystallization to give single diastereomeric products with 99% ee. The cyclopentenedione with a cinnamyl substituent provided product **4n** with 90% ee, albeit as an 85:15 mixture. Ester as well as ether moieties were tolerated under the current catalyst system to give diastereomerically pure products **4o** and **4p** with excellent stereoselectivities. Furthermore, the use of ethylcyclopentenediones also provided enantiomerically and diastereomerically pure products **4q**–**s** in good to excellent yields.

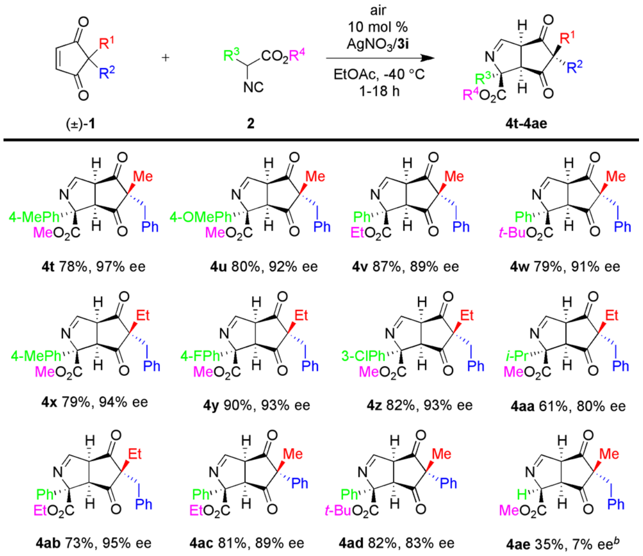
Scheme 3 summarizes the scope of isocyanoacetates, where the ester moiety and the *α*-position were varied. The catalytic asymmetric desymmetrization reaction proceeded smoothly with *α*-Ph derivatives (**4t** and **4u**) and ethyl (**4v**) and *tert*-butyl (**4w**) ester moieties with excellent selectivities. Similar reactivity and selectivity patterns were also observed for ethylcyclopentenediones (**4x**–**z**). The use of *α*-*i*-Pr isocyanoacetate provided a single diastereomeric product **4aa** with 80% ee. Likewise, isocyanides with other *α*-ester moieties afforded the desymmetrized products (**4ab**–**ad**) with good to excellent selectivities. The limitation of the current desymmetrization catalyst system, however, exists in the use of methyl isocyanoacetate without *α*-substitution, where the diastereomerically pure racemic product **4ae** was obtained in 35% yield.

Scheme 2. Scope of Cyclopentenediones in the $AgNO_3$-Catalyzed [3 + 2] Cycloaddition Reaction[a]



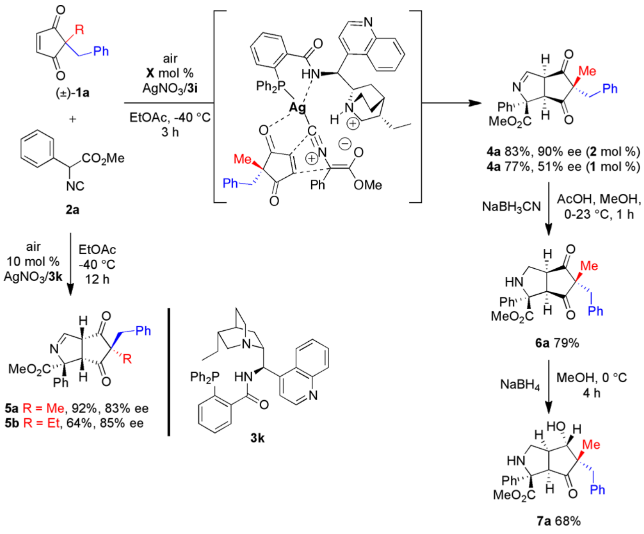
[a] Reaction with **1** (0.24 mmol) and **2a** (0.20 mmol) in EtOAc (0.10 M) under air. Unless stated otherwise, a single diastereomeric product **4** was observed. [b] Inseparable mixture with 92:8 dr. [c] After recrystallization from a crude mixture with 84:16 dr and 90% ee. [d] After recrystallization from a crude mixture with 92:8 dr and 91% ee. [e] Inseparable mixture with 85:15 dr.

Scheme 3. Scope of Isocyanoacetates in the $AgNO_3$-Catalyzed [3 + 2] Cycloaddition Reaction[a]



[a] Reaction with **1** (0.24 mmol) and **2** (0.20 mmol) in EtOAc (0.10 M) under air. Unless stated otherwise, a single diastereomeric product **4** was observed. [b] The crude mixture was contaminated with unidentified byproducts.

Scheme 4. Application of the Desymmetrization Reaction and Synthetic Manipulation of Products



The use of pseudoenantiomeric catalyst **3k** led to the formation of the desired products **5a** and **5b** with 83−85% ee (Scheme 4). The catalyst loading was further investigated in reactions on a 1 mmol scale, which revealed that a minimum catalyst loading of 2 mol % was needed to achieve the formation of products with ≥90% ee. Synthetic manipulation of product **4a** was also possible. Thus, the imine moiety of **4a** could be selectively reduced to give bicyclic pyrrolidine **6a** in 79% yield. A subsequent reduction delivered another regio- and stereoselective reduction of a less sterically congested ketone moiety to **7a** in 68% yield. While more work needs to be done to determine the detailed reaction mechanism, since no conjugate addition products were observed by NMR monitoring, it is more likely that a concerted [3 + 2] reaction pathway is involved. The preorganization of the silver catalyst via an electrostatic interaction between the bridgehead ammonium salt and the enolate may explain the observed stereoselectivities.[18]

In summary, we have discovered a practical silver Lewis acid catalyst system that delivers highly enantio- and diastereoselective [3 + 2] cycloaddition reactions between isocyanoacetates and cyclopentenediones via desymmetrization. The developed catalyst system notably tolerates moisture and air, defying the typical sensitivity issues associated with chiral Lewis acid catalysts. The use of $AgNO_3$ makes the current catalyst system easy to use without special care since the active catalysts are generated while in the presence of isocyanides. The possible use of a catalyst loading as low as 2 mol % combined with the use of class III solvents should facilitate the catalyst discovery-to-process in pharmaceutical development. Additional studies to extend the chiral Ag(I) catalyst system to other isocyanide transformations are currently underway, and our results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00590.

Experimental procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1584890 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, 2008; Vols. *1 and 2*.

(2) For selected reviews, see: (a) *Silver in Organic Chemistry*; Harmata, M., Ed.; Wiley: Hoboken, NJ, 2010. (b) Munoz, M. P. *Chem. Soc. Rev.* **2014**, *43*, 3164. (c) Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, *44*, 8124. (d) Lo, V. K.-Y.; Chan, A. O.-Y.; Che, C.-M. *Org. Biomol. Chem.* **2015**, *13*, 6667. (e) Sekine, K.; Yamada, T. *Chem. Soc. Rev.* **2016**, *45*, 4524.

(3) (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Org. Chem.* **1990**, *55*, 5935. (b) Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1991**, *32*, 2799. (c) Soloshonok, V. A.; Hayashi, T.; Ishikawa, K.; Nagashima, N. *Tetrahedron Lett.* **1994**, *35*, 1055.

(4) (a) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723. (b) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319. (c) Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 892. (d) Yanagisawa, A.; Terajima, Y.; Sugita, K.; Yoshida, K. *Adv. Synth. Catal.* **2009**, *351*, 1757. (e) Yanagisawa, A.; Miyake, R.; Yoshida, K. *Eur. J. Org. Chem.* **2014**, *2014*, 4248.

(5) (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (c) Josephsohn, N. S.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 2711. (d) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532. (e) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230. (f) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961. (g) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570.

(6) For recent reviews, see: (a) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132. (b) Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G. *Chem. Commun.* **2010**, *46*, 4043. (c) Pellissier, H. *Chem. Rev.* **2016**, *116*, 14868.

(7) For recent reviews, see: (a) Chakrabarty, S.; Choudhary, S.; Doshi, A.; Liu, F.-Q.; Mohan, R.; Ravindra, M. P.; Shah, D.; Yang, X.; Fleming, F. F. *Adv. Synth. Catal.* **2014**, *356*, 2135. (b) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698. (c) Song, B.; Xu, B. *Chem. Soc. Rev.* **2017**, *46*, 1103.

(8) For a recent review, see: Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330.

(9) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346.

(10) (a) Aikawa, K.; Okamoto, T.; Mikami, K. *J. Am. Chem. Soc.* **2012**, *134*, 10329. (b) Manna, M. S.; Mukherjee, S. *Chem. Sci.* **2014**, *5*, 1627. (c) Dou, X.; Lu, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 6739. (d) Zhi, Y.; Zhao, K.; Wang, A.; Englert, U.; Raabe, G.; Enders, D. *Adv. Synth. Catal.* **2017**, *359*, 1867.

(11) Manna, M. S.; Mukherjee. *J. Am. Chem. Soc.* **2015**, *137*, 130.

(12) Walker, S. E.; Lamb, C. J. C.; Beattie, N. A.; Nikodemiak, P.; Lee, A.-L. *Chem. Commun.* **2015**, *51*, 4089.

(13) (a) Das, T.; Saha, P.; Singh, V. K. *Org. Lett.* **2015**, *17*, 5088. (b) Liu, H.-C.; Liu, K.; Xue, Z.-Y.; He, Z.-L.; Wang, C.-J. *Org. Lett.* **2015**, *17*, 5440.

(14) For a pictorial representation of the dissolution of $AgNO_3$ by isocyanides, see the Supporting Information.

(15) *Q3C—Tables and List Guidance for Industry*; U.S. Food and Drug Administration: Silver Spring, MD, 2017

(16) (a) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 1710. (b) Ortin, I.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3462. (c) de la Campa, R.; Ortin, I.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 4895. (d) de la Campa, R.; Gammack Yamagata, A. D.; Ortin, I.; Franchino, A.; Thompson, A. L.; Odell, B.; Dixon, D. J. *Chem. Commun.* **2016**, *52*, 10632. (e) Shao, P.-L.; Liao, J.-Y.; Ho, Y. A.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5435. (f) Liao, J.-Y.; Shao, P.-L.; Zhao, Y. *J. Am. Chem. Soc.* **2015**, *137*, 628. (g) Cheng, H.; Zhang, R.; Yang, S.; Wang, M.; Zeng, X.; Xie, L.; Xie, C.; Wu, J.; Zhong, G. *Adv. Synth. Catal.* **2016**, *358*, 970.

(17) No isocyano aldol reaction of acetone was observed.

(18) One of the referees suggested the possibility of $\pi-\pi$ interactions between two reactants since the bicylic products with two aryl groups were obtained with higher ee values than the alkyl-substituted ones. This is a valid mechanistic point, and we are looking into such interactions using a computational approach. We thank the reviewer for providing valuable mechanistic insight.