HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2020 March 13.

Published in final edited form as:

J Am Chem Soc. 2019 March 13; 141(10): 4199–4203. doi:10.1021/jacs.8b13757.

Enantioselective Conia-Ene-Type Cyclizations of Alkynyl Ketones through Cooperative Action of $B(C_6F_5)_3$, *N*-Alkylamine and a Zn-Based Catalyst

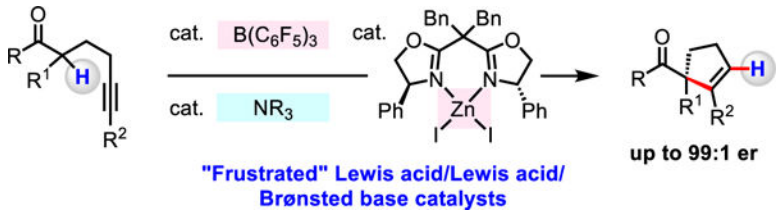
Min Cao, **Ahmet Yesilcimen**, and **Masayuki Wasa***

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Abstract

An efficient and highly enantioselective Conia-ene-type process has been developed. Reactions are catalyzed by a combination of $B(C_6F_5)_3$, an *N*-alkylamine and a BOX–ZnI_2 complex. Specifically, through cooperative action of $B(C_6F_5)_3$ and amine, ketones with poorly acidic *α*-C–H bonds can be converted in situ to the corresponding enolates. Subsequent enantioselective cyclization involving a BOX–ZnI_2-activated alkyne leads to the formation of various cyclopentenes in up to 99% yield and 99:1 er.

Graphical Abstract



Cooperative acid/base catalysis may be used to promote an enantioselective reaction between an in situ generated, acid-activated electrophile and a base-activated nucleophile.[1,2] One of the key challenges in developing such transformations is to find a way for bypassing undesirable mutual quenching. Although one possible solution is to avoid utilizing a combination that exhibits high affinity (i.e., hard–hard or soft–soft pairing),[1,2] this approach has been confined to cases that involve weakly or moderately acidic and/or basic catalysts along with substrates that are acid- or base-sensitive. Development of highly efficient and unquenchable cooperative catalyst systems that are capable of promoting enantioselective reactions between relatively unactivated starting materials stands as a largely unresolved challenge.

***Corresponding Author** wasa@bc.edu.

The authors declare no competing financial interest.

Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

The application of frustrated Lewis pairs (FLPs), consisting of hindered and electronically disparate Lewis acids and Lewis bases, has recently emerged as an enabling strategy for overcoming undesirable mutual quenching.[3,4] Furthermore, FLPs that are comprised of Lewis acidic $B(C_6F_5)_3$ and a Brønsted basic *N*-alkylamine catalyst have been shown to promote Mannich-type and α-amination reactions with ketone, ester or amide pro-nucleophiles (pK_a ~20–30).[5] An ammonium ion derived from an *N*-alkylamine catalyst is thought to serve as a poorly activating Brønsted acid catalyst;[1,2] these methods therefore demand acid-sensitive electrophiles such as *N*-Boc-benzaldimines or dimethyl azodicarboxylate. We reasoned that catalyst systems comprised of $B(C_6F_5)_3$, an *N*-alkylamine and a Lewis acid co-catalyst for electrophile activation might pave the way for development of reactions between unactivated pro-nucleophiles and electrophiles.

Enantioselective cycloadditions of 1,3-dicarbonyl compounds with a tethered alkyne moiety (5-*exo-dig* and 5-*endo-dig* processes) offer access to valuable five-membered ring structures that bear an *exo*-methylene moiety (e.g., **I** to **II**; Figure 1A) or cyclopentene derivatives.[6–9] These "direct" Conia-ene-type reactions can be promoted by cooperative Lewis acid/Lewis acid catalysts (e.g., Pd/Yb-, La/Ag-, Zn/Yb-based),[7] or enantiomerically pure Lewis basic amine/Lewis acid catalysts (e.g., Cu-, Ag-based).[8] Such transformations allow for in situ generation of an enolate equivalent by Lewis acid or Lewis base catalyzed deprotonation, in addition to an electrophilic alkyne unit by Lewis acid activation.[4] Nonetheless, the requisite weakly to moderately acidic and/or basic catalysts render the approach confined to readily enolizable 1,3-dicarbonyl compounds (e.g., **I**; pK_a ~10).[6–8] With catalysts that are more strongly acidic and/or basic and capable of deprotonating less acidic ketones (pK_a ~20), mutual quenching can be an issue.[1,2] Consequently, pre-formation of silicon enolate is needed for enantioeselective R_3P/Au-catalyzed (5-*endo-dig*) cyclization of ketones (**III** to **IV**; Figure 1B).[10] Synergetic catalyst systems that promote direct enantioselective Conia-ene-type processes with mono-carbonyl compounds remain unprecedented. Herein, we describe enantioselective direct Conia-ene-type reaction of ketones promoted by cooperative action of $B(C_6F_5)_3$, an *N*-alkylamine and a chiral Lewis acid co-catalyst (Figure 1C).

In contemplating ways to design an enantioselective method for cyclization of ketones that contain an alkyne unit (**1**), we envisioned a catalyst system that is comprised of a strongly Lewis acidic $B(C_6F_5)_3$, a Brønsted basic *N*-alkylamine, and a chiral Lewis acid co-catalyst (Figure 1C). By employing structurally and electronically different organoborane and chiral Lewis acid co-catalyst that could have overlapping functions, we might be able to control the ability of $B(C_6F_5)_3$ to serve as a carbonyl activator, and use the chiral Lewis acid co-catalyst to elevate alkyne reactivity (**V**). We surmised that *N*-alkylamine could deprotonate $B(C_6F_5)_3$-activated ketone of **1**, generating an enolate and an ammonium ion (**VI**). In the meantime, a chiral Lewis acid co-catalyst (ML*) would activate the alkyne unit (**VI**). An ensuing enantiodetermining 5-*endo-dig* cyclization of the enolate and the alkyne would deliver **VII**. Subsequent protonation of C–ML* bond by the ammonium ion would afford the desired cyclopentenyl product **2**. One key advantage provided by the untethered catalyst system would be that efficiency and stereoselectivity might be optimized through rapid evaluation of readily accessible Lewis acids, chiral ligands, and *N*-alkylamines.

To identify an optimal catalyst combination, we probed the ability of $B(C_6F_5)_3$, 1,2,2,6,6-pentamethylpiperidine (PMP), and various chiral Lewis acid/ligand complexes to catalyze the cyclization of 1-phenylnon-5-yn-1-one **1a** (CH_2Cl_2, 12 h, 22 °C), to generate **2a** (Table 1).[11] The combination of 10 mol% ZnI_2 and Ph–PyBOX (**L1**) or Ph–DBFOX (**L2**) afforded **2a** in 20% and 7% yield, and 83:17 and 55:45 er, respectively. With Ph–BOX (**L3**) as the ligand, the desired product was generated in >95% yield and 89:11 er. Catalysts derived from alkyl-substituted **L4** (10% yield and 75:25 er) and **L5** (6% yield, 71:28 er) were less effective. Evaluation of Ph–BOX ligands with varying 2,2'-substiutents (cyclopropyl (**L6**), diisopropyl (**L7**), and dibenzyl (**L8**)) led us to establish that **L8** is the most effective, providing **2a** in >95 % yield and 97:3 er.[12]

The amount of a bis-oxazoline ligand had a notable impact on efficiency and er. In the absence of **L8**, under otherwise identical conditions, *rac*-**2a** was isolated in >95% yield;[13] as a consequence, there was diminution in enantioselectivity when 10 mol% of ZnI_2 and 8.0 mol% of **L8** was used (**2a** in >95% yield, 92:8 er). On the other hand, with excess **L8** (13 mol%), **2a** was obtained in <5% yield, suggesting that the Lewis basic oxazoline units of **L8** can deactivate $B(C_6F_5)_3$. Preformed and purified ZnI_2/**L8** complex may be used with similar effect.[14]

Next, we set out to identify an effective organoborane and Brønsted base catalysts, and optimize other reaction parameters (Table 2). Whereas with Et_3N, **2a** was obtained in >95% yield and 97:3 er (entry 1), none of the desired product could be detected with DBU as the base (entry 2). With less $B(C_6F_5)_3$ (7.5 mol%), PMP (15 mol%), ZnI_2/**L8** (7.5 mol%), efficiency suffered but not enantioselectivity (90% yield, 97:3 er; entry 4). Efficiency improved at 40 °C (entry 5), allowing catalyst loading to be reduced to 5.0 mol% $B(C_6F_5)_3$, 10 mol% PMP and 5.0 mol% ZnI_2/**L8**; under these conditions, **2a** was produced in 92% yield and 97:3 er (entry 6). No product was generated without the Brønsted base, the organoborane catalyst or the ZnI_2/**L8** (entries 7–9); the same was the case when the smaller BF_3•OEt_2 or the less acidic BPh_3 were used (entries 10–11). Thus, the appropriately acidic $B(C_6F_5)_3$, sizeable and electron-rich PMP, together with sterically demanding ZnI_2/**L8** complex emerged as the most effective combination.

A variety of 1-phenyl ketones with different alkyne substituents proved to be suitable substrates (**2a**–**2i**; Table 3). With 1-phenylhex-5-yn-1-one, containing a terminal alkyne moiety (R = H), the transformation was inefficient and moderately enantioselective (10% yield, 70:30 er).[15] In contrast, 1-phenylhept-5-yn-1-one, which bears an internal alkyne (R = Me), was converted to **2b** in 96% yield and 82:18 er. Reactions involving substrates that carry a larger ethyl, *n*-propyl, *n*-butyl, and *iso*-butyl substituent, afforded the desired products in >95% yield and 96:4–97:3 er (**2a**, **2c**–**2e**). Although benzyl-substituted substrate furnished **2f** in 82% yield and 98:2 er, phenyl-substituted substrate was less efficient (**2g**, 50% yield, 91:9 er). As indicated by the formation of **2h** (97% yield, 94:6 er) and **2i** (94% yield, 97:3 er), the presence of a carboxylic ester or a monosubstituted alkene is tolerated.

We then investigated reactions with different aryl- and alkyl-substituted ketones (Table 4). 2-Methoxyphenyl- and 4-bromophenyl-substituted ketones gave **2j** (95% yield, 93:7 er) and **2k** (97% yield, 97:3 er), respectively. The process involving indanone derivative did not afford

2l when PMP was employed as a Brønsted base catalyst, probably because it is too hindered to deprotonate a tertiary C–H bond within a $B(C_6F_5)_3$-activated ketone. In the case of using less hindered 1-methylpiperidine, **2l**, which possesses an α-quaternary carbon center was produced in 98% yield and 99:1 er. Tetralone-derived **2m** was formed inefficiently (20% yield) but in 98:2 er, perhaps an indication of severe steric repulsion between the *n*-propyl substituent and the tetralone ring. Thus, we were able to convert a Me-substituted substrate to **2n** in 73% yield and 91:9 er. Thiophene-substituted **2o** (99% yield, 98:2 er) and furan-substituted **2p** (99% yield, 97:3 er) provide further evidence regarding the approach's notable scope. Transformations with alkyl ketones were similarly effective, as represented by **2q** (91% yield, 95:5 er) and **2r** (77% yield, 96:4 er). Cyclopentanone derivative **2s** was generated with 1-methylpiperidine as the Brønsted base, but in diminished er (82% yield, 80:20 er).

The method is readily scalable. Treatment of 1.5 g (7.0 mmol) of **1a** with 2.5 mol% $B(C_6F_5)_3$, 5.0 mol% PMP and 2.5 mol% ZnI_2/**L8** (CH_2Cl_2, 24 h, 40 °C) afforded **2a** in 94% yield (6.6 mmol, 1.4 g) and 97:3 er (Scheme 1). Moreover, we discovered that cycloaddition of 1-phenylhept-6-yn-1-one (**3a**) (5-*exo*-*dig*) is facilitated by $B(C_6F_5)_3$, 1-methylpiperidine and ZnI_2/**L8** to deliver *exo*-methylene-substituted cyclopentane **4a** in 98% yield but just 68:32 er. Studies are underway to enhance the applicability of the approach.

To summarize, we have designed an efficient and enantioselective Conia-ene-type reaction by implementing the cooperative action of a three-component catalyst system, which consists of a pair of Lewis acids and a Brønsted basic amine. We show that by tuning of different features of Lewis acids that possess overlapping functions, it is possible to engage Lewis acid catalysts to serve as an activator of a carbonyl group or an activator of electron-rich alkyne. Accordingly, efficiency and stereoselectivity of C–C bond forming reactions between in situ generated enolate and chiral Lewis acid-activated alkyne can be conveniently enhanced without significant loss in er, which might arise due to intervention by an achiral Lewis acid component. The principles outlined herein, entailing separate and independently operational Lewis acidic co-catalysts and a Brønsted base catalyst, provide a rational framework for further development of processes involving weakly acid- and/or base-sensitive substrates. Studies aimed at achieving these objectives are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements.

Financial support was provided by the NIH (GM-128695) and Boston College. We thank Professor Amir H. Hoveyda (Boston College) for helpful discussions. We also thank Dr. Bo Li and Dr. Malte S. Mikus (Boston College) for X-ray crystallographic analysis.

References

(1). For selected reviews on enantioselective cooperative catalysis, see: (a) Yamamoto H; Futatsugi K "Designer Acids": Combined Acid Catalysis for Asymmetric Synthesis. Angew. Chem., Int. Ed 2005, 44, 1924–1942.(b)Paull DH; Abraham CJ; Scerba MT; Alden-Danforth E; Lectka T

Bifunctional Asymmetric Catalysis: Cooperative Lewis Acid/Base Systems. Acc. Chem. Res 2008, 41, 655–633. [PubMed: 18402470] (c)Kobayashi S; Mori Y; Fossey JS; Salter MM Catalytic Enantioselective Formation of C–C Bonds by Addition to Imines and Hydrazones: A Ten-Year Update. Chem. Rev 2011, 111, 2626–2704. [PubMed: 21405021] (d)Trost BM; Bartlett MJ ProPhenol-Catalyzed Asymmetric Additions by Spontaneously Assembled Dinuclear Main Group Metal Complexes. Acc. Chem. Res 2015, 48, 688–701. [PubMed: 25650587] (e)Shibasaki M; Kumagai N in Cooperative Catalysis: Designing Efficient Catalysts for Synthesis, Peters R, Eds.; Wiley-VCH: New York, 2015; Chapter 1.

(2). For selected reviews on enantioselective non-covalent catalysis, see: (a) Hashimoto T; Maruoka K Recent Development and Application of Chiral Phase-Transfer Catalysts. Chem. Rev 2007, 107, 5656–5682. [PubMed: 18072806] (b)Ooi T; Maruoka K Recent Advances in Asymmetric Phase-Transfer Catalysis. Angew. Chem., Int. Ed 2007, 46, 4222–4266.(c)Adair G; Mukherjee S; List B TRIP - A powerful Brønsted acid catalyst for asymmetric synthesis. Aldrichimica Acta 2008, 41, 31–39.(d)Zhang Z; Schreiner PR (Thio)urea organocatalysis—What can be learnt from anion recognition? Chem. Soc. Rev 2009, 38, 1187–1198. [PubMed: 19421588] (e)Phipps RJ; Hamilton GL; Toste FD The progression of chiral anions from concepts to applications in asymmetric catalysis. Nat. Chem 2012, 4, 603–614. [PubMed: 22824891] (f)Brak K; Jacobsen EN Asymmetric Ion-Pairing Catalysis. Angew. Chem., Int. Ed 2013, 52, 534–561.(g)Neel AJ; Hilton MJ; Sigman MS; Toste FD Exploiting non-covalent π interactions for catalyst design. Nature 2017, 543, 637–646. [PubMed: 28358089]

(3). For reviews of frustrated Lewis pair chemistry, see: (a) Frustrated Lewis Pairs I; Stephan DW; Erker G Eds.; Springer Press: New York, 2013; Vol. 332.(b)Frustrated Lewis Pairs II: Expanding the Scope; Erker G; Stephan DW Eds.; Springer: Berlin, 2013; Vol. 334.(c)Ashley AE; O'Hare D FLP-Mediated Activations and Reductions of CO_2 and CO. Top. Curr. Chem 2013, 334, 191–218. [PubMed: 23114497] (d)Feng X; Du H Metal-free asymmetric hydrogenation and hydrosilylation catalyzed by frustrated Lewis pairs. Tetrahedron Lett 2014, 55, 6959–6964. (e)Stephan DW; Erker G Frustrated Lewis Pair Chemistry: Development and Perspectives. Angew. Chem., Int. Ed 2015, 54, 6400–6441.(f)Stephan DW Frustrated Lewis Pairs J. Am. Chem. Soc 2015, 137, 10018–10032. [PubMed: 26214241] (g)Oestreich M; Hermeke J; Mohr J A unified survey of Si–H and H–H bond activation catalysed by electron-deficient boranes. Chem. Soc. Rev 2015, 44, 2202–2220. [PubMed: 25679769] (h)Stephan DW The broadening reach of frustrated Lewis pair chemistry. Science 2016, 354, aaf7229.

(4). For activation of alkynes by $B(C_6F_5)_3$, see: (a) Dureen MA; Brown CC; Stephan DW Addition of Enamines or Pyrroles and $B(C_6F_5)_3$ "Frustrated Lewis Pairs" to Alkynes. Organometallics 2010, 29, 6422–6432.(b)Hansmann MM; Melen RL; Rominger F; Hashmi ASK; Stephan DW Activation of Alkynes with $B(C_6F_5)_3$–Boron Allylation Reagents Derived from Propargyl Esters. J. Am. Chem. Soc 2014, 136, 777–782. [PubMed: 24354408]

(5). (a)Chan JZ; Yao W; Hastings BT; Lok CK; Wasa M Direct Mannich-Type Reactions Promoted by Frustrated Lewis Acid/Brønsted Base Catalysts. Angew. Chem., Int. Ed 2016, 55, 13877–13881. (b)Shang M; Wang X; Koo SM; Youn J; Chan JZ; Yao W; Hastings BT; Wasa M Frustrated Lewis Acid/Brønsted Base Catalysts for Direct Enantioselective α-Amination of Carbonyl Compounds. J. Am. Chem. Soc 2017, 139, 95–98. [PubMed: 27983825] (c)Shang M; Cao M; Wang Q; Wasa M Enantioselective Direct Mannich-Type Reaction Catalyzed by Frustrated Lewis Acid/Brønsted Base Complexes. Angew. Chem., Int. Ed 2017, 56, 13338–13526.

(6). (a)Conia JM; Perchec PL The Thermal Cyclisation of Unsaturated Carbonyl Compounds. Synthesis 1975, 1, 1–19.(b)Hack D; Blümel M; Chauhan P; Philipps AR; Enders D Catalytic Conia-ene and related reactions. Chem. Soc. Rev 2015, 44, 6059–6093. [PubMed: 26031492]

(7). (a)Corkey BK; Toste FD Catalytic Enantioselective Conia-Ene Reaction. J. Am. Chem. Soc 2005, 127, 17168–17169. [PubMed: 16332048] (b)Matsuzawa A; Mashiko T; Kumagai N; Shibasaki M La/Ag Heterobimetallic Cooperative Catalysis: A Catalytic Asymmetric Conia-Ene Reaction. Angew. Chem., Int. Ed 2011, 123, 7758–7761.(c)Suzuki S; Tokunaga E; Reddy DS; Matsumoto T; Shiro M; Shibata N Enantioselective 5-endo-dig Carbocyclization of *β*-Ketoesters with Internal Alkynes Employing a Four Component Catalyst System. Angew. Chem., Int. Ed 2012, 51, 4131–4135.

(8). (a)Yang T; Ferrali A; Sladojevich F; Campbell L; Dixon DJ Brønsted Base/Lewis Acid Cooperative Catalysis in the Enantioselective Conia-Ene reaction. J. Am. Chem. Soc 2009, 131,

9140–9141. [PubMed: 19527029] (b)Shaw S; White JD A New Iron (III)–Salen Catalyst for Enantioselective Conia-ene Carbocyclization. J. Am. Chem. Soc 2014, 136, 13578–13581. [PubMed: 25213211] (c)Blümel M; Hack D; Ronkartz L; Vermeeren C; Enders D Development of an enantioselective amine–silver co-catalyzed Conia-ene reaction. Chem. Commun 2017, 53, 3956–3959.

(9). For selected examples on application of Conia-ene-type reaction, see: (a) >Staben ST; Kennedy-Smith JJ; Huang D; Corkey BK; LaLonde RL; Toste FD Gold (I)-Catalyzed Cyclizations of Silyl Enol Ethers: Application to the Synthesis of (+)-Lycopladine A. Angew. Chem., Int. Ed 2006, 45, 5991–5994.(b)Tsuji H; Yamagata KI; Itoh Y; Endo K; Nakamura M; Nakamura E Indium-Catalyzed Cycloisomerization of ω-Alkynyl-β-ketoesters into Six- to Fifteen-Membered Rings. Angew. Chem., Int. Ed 2007, 46, 8060–8062.(c)Takahashi K; Midori M; Kawano K; Ishihara J; Hatakeyama S Entry to Heterocycles Based on Indium-Catalyzed Conia-Ene Reactions: Asymmetric Synthesis of (–)-Salinosporamide A. Angew. Chem., Int. Ed 2008, 47, 6244–6246. (d)Liu X; Lee CS Total synthesis of (–)-Teucvidin. Org. Lett 2012, 14, 2886–2889. [PubMed: 22594711] (e)Huwyler N; Carreira EM Total Synthesis and Stereochemical Revision of the Chlorinated Sesquiterpene (±)-Gomerone C. Angew. Chem., Int. Ed 2012, 51, 13066–13069. (f)Persich P; Llaveria J; Lhermet R; de Haro T; Stade R; Kondoh A; Fürstner A Increasing the Structural Span of Alkyne Metathesis. Chem. Eur. J 2013, 19, 13047–13058. [PubMed: 24038738] (g)Xiong X; Li Y; Lu Z; Wan M; Deng J; Wu S; Shao H; Li A Synthesis of the 6, 6, 5, 7-tetracyclic core of daphnilongeranin B. Chem. Commun 2014, 50, 5294–5297.(h)Hartrampf FW; Furukawa T; Trauner D A Conia-Ene-Type Cyclization under Basic Conditions Enables an Efficient Synthesis of (–)-Lycoposerramine R. Angew. Chem., Int. Ed 2017, 56, 893–896.(i)Ye Q; Qu P; Snyder SA Total Syntheses of Scaparvins B, C, and D Enabled by a Key C–H Functionalization. J. Am. Chem. Soc 2017, 139, 18428–18431. [PubMed: 29227651] (j)Hartrampf FW; Trauner D Total Synthesis of Lycopladine A and Carinatine A via a Base-Mediated Carbocyclization. J. Org. Chem 2017, 82, 8206–8212. [PubMed: 28671469]

(10). (a)Corkey BK; Toste FD Palladium-Catalyzed Enantioselective Cyclization of Silyloxy-1, 6-Enynes. J. Am. Chem. Soc 2007, 129, 2764–2765. [PubMed: 17305344] (b)Brazeau JF; Zhang S; Colomer I; Corkey BK; Toste FD Enantioselective Cyclizations of Silyloxyenynes Catalyzed by Cationic Metal Phosphine Complexes. J. Am. Chem. Soc 2012, 134, 2742–2749. [PubMed: 22296571]

(11). For a comprehensive evaluation of Fe, Cu, Ag, Mg, In, Yb, Au-based Lewis acids and their complexes with various chiral ligands, see the SI.

(12). For the determination of absolute configuration for product 2a, see the SI. The absolute configuration for the other products was assigned in analogy.

(13). For the data involving evaluation of achiral Lewis acid co-catalysts, see the SI.

(14). (a)Thorhauge J; Roberson M; Hazell RG; Jørgensen KA On the Intermediates in Chiral Bis(oxazoline)copper(II)-Catalyzed Enantioselective Reactions—Experimental and Theoretical Investigations. Chem. Eur. J 2002, 8, 1888–1898. [PubMed: 12007099] (b)Desimoni G; Faita G; Jørgensen KA C_2-Symmetric Chiral Bis(oxazoline) Ligands in Asymmetric Catalysis. Chem. Rev 2011, 111, 284–437.

(15). For the experimental results involving the enantioselective cyclization of 1-phenylhex-5-yn-1-one, see the SI.

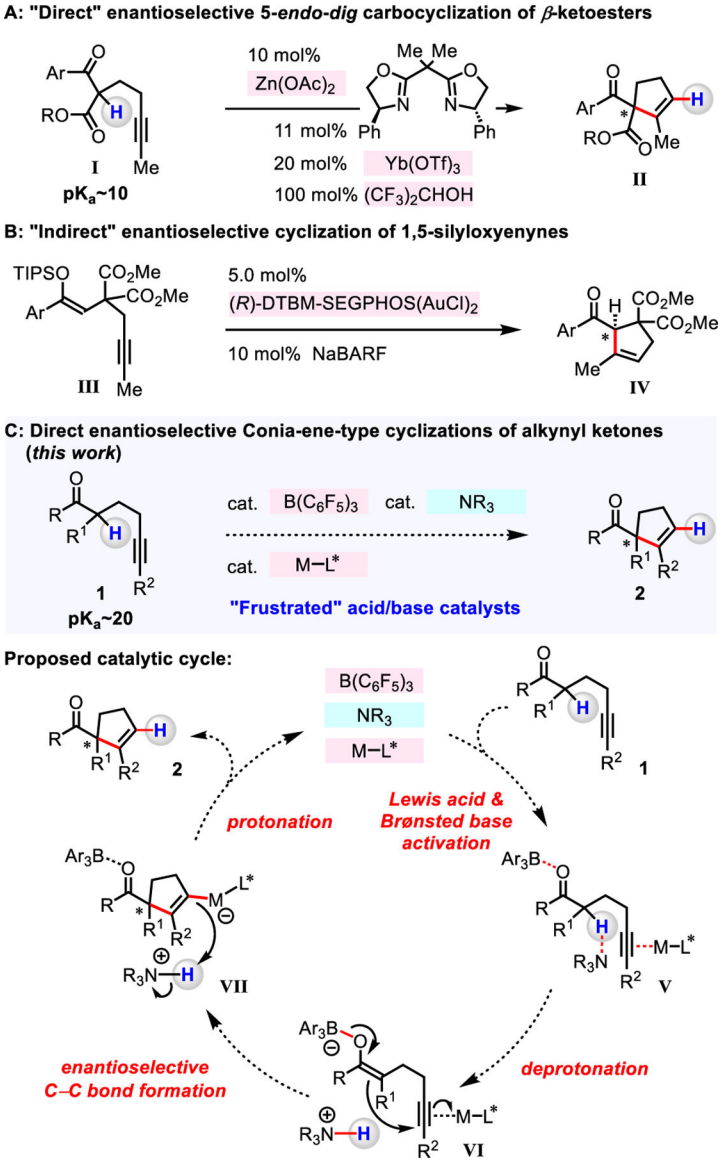
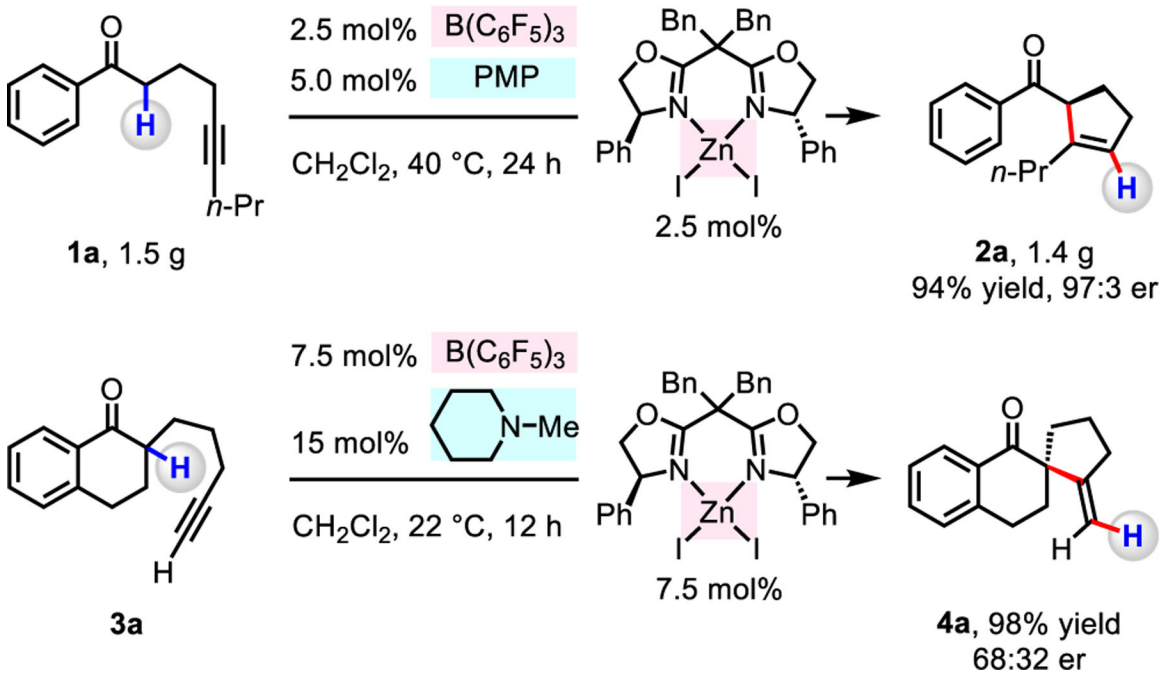


Figure 1.
Enantioselective 5-*endo-dig* cycloadditions.

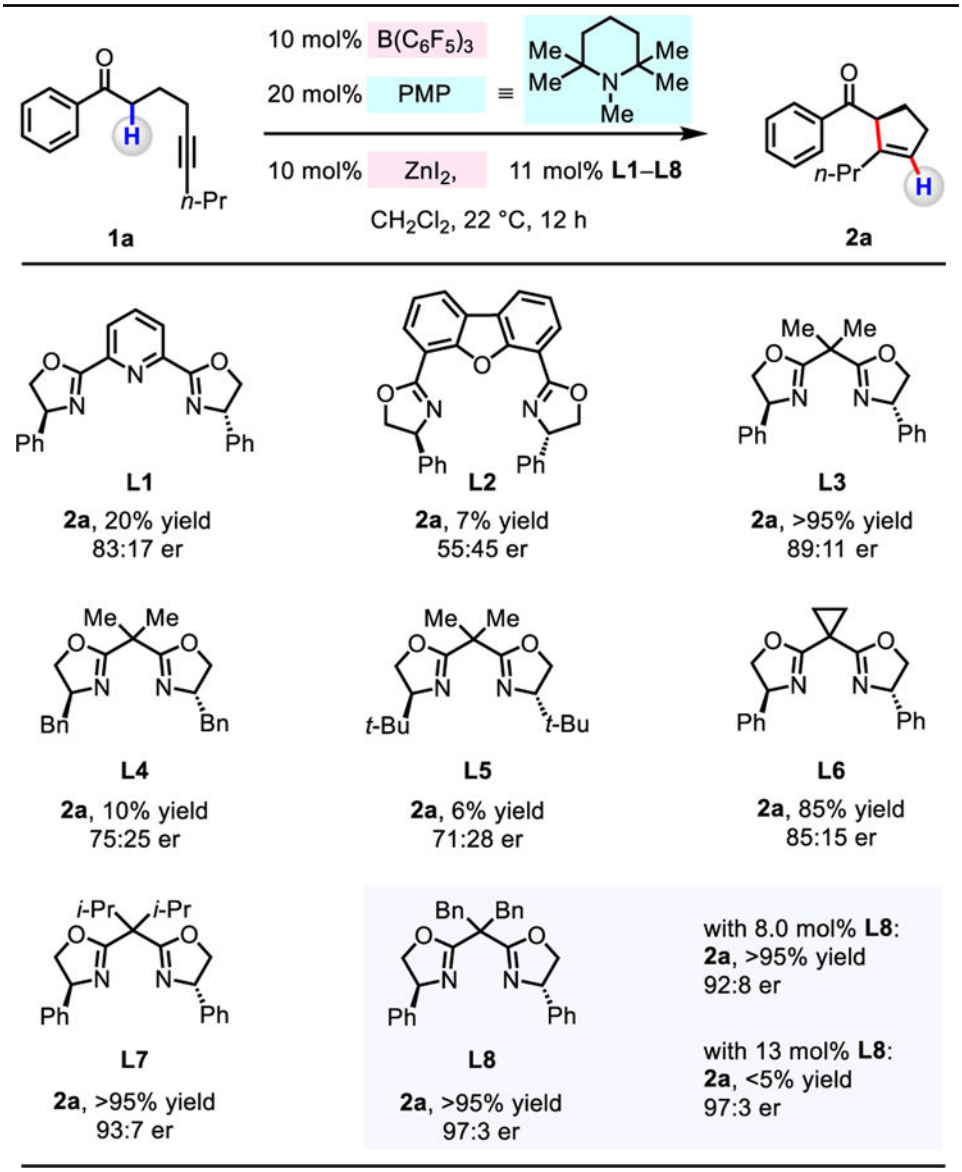


Scheme 1.

Scale-up experiments and 5-*exo-dig* cycloaddition of **3a**

Table 1.

Evaluation of Bis-oxazoline Ligands [a,b]

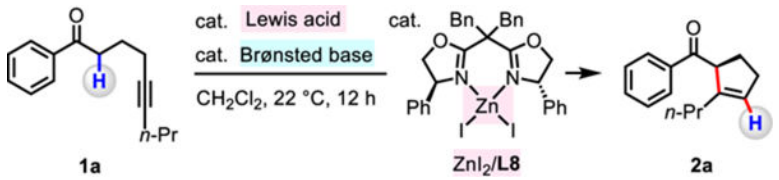


[a]Conditions: 1-phenylnon-5-yn-1-one (**1a**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (20 mol%), ZnI_2 (10 mol%), bis-oxazoline ligand (11 mol%), CH_2Cl_2 (1.0 mL), under N_2, 22 °C, 12 h.

[b]Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product.

Table 2.

Evaluation of Reaction Parameters [a,b]



entry	Lewis acid (mol%)	Brønsted base (mol%)	ZnI_2/L8 (mol%)	yield of 2a (%)	er
1	$B(C_6F_5)_3$ (10)	NET_3 (20)	10	>95	97:3
2	$B(C_6F_5)_3$ (10)	DBU (20)	10	0	ND
3	$B(C_6F_5)_3$ (10)	PMP (20)	10	>95	97:3
4	$B(C_6F_5)_3$ (7.5)	PMP (15)	7.5	90	97:3
5[c]	$B(C_6F_5)_3$ (7.5)	PMP (15)	7.5	>95	97:3
6[c]	$B(C_6F_5)_3$ (5.0)	PMP (10)	5.0	92	97:3
7	$B(C_6F_5)_3$ (5.0	none	5.0	0	ND
8	none	PMP (10)	5.0	0	ND
9	$B(C_6F_5)_3$ (5.0)	PMP (10)	0	0	ND
10	$BF_3{\cdot}OEt_2$ (5.0)	PMP (10)	5.0	0	ND
11	BPh_3 (5.0)	PMP (10)	5.0	0	ND

[a]Conditions: 1-phenylnon-5-yn-1-one (**1a**, 0.2 mmol), organoborane, Brønsted base, ZnI_2/**L8** complex, CH_2Cl_2 (1.0 mL), under N_2, 22 °C, 12 h.

[b]Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product.

[c]The reaction mixture was allowed to stir at 40 °C.

Table 3.

Conia-Ene-Type Reactions with Different Alkyne Substituents [a,b]

[a]Conditions: Alkynyl ketone (**1a-1d**, **1h**, **1i**; 0.2 mmol), $B(C_6F_5)_3$ (7.5 mol%), 1,2,2,6,6-pentamethylpiperidine (15 mol%), ZnI_2/**L8** (7.5 mol%), CH_2Cl_2 (1.0 mL), under N_2, 40 °C, 12 h. [b]Yield of isolated and purified product. The er values were determined by HPLC analysis of the purified product. [c]Alkynyl ketone (**1e-1g**; 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (20 mol%), ZnI_2/**L8** (10 mol%), $ClCH_2CH_2Cl$ (1.0 mL), under N_2, 60 °C, 24 h.

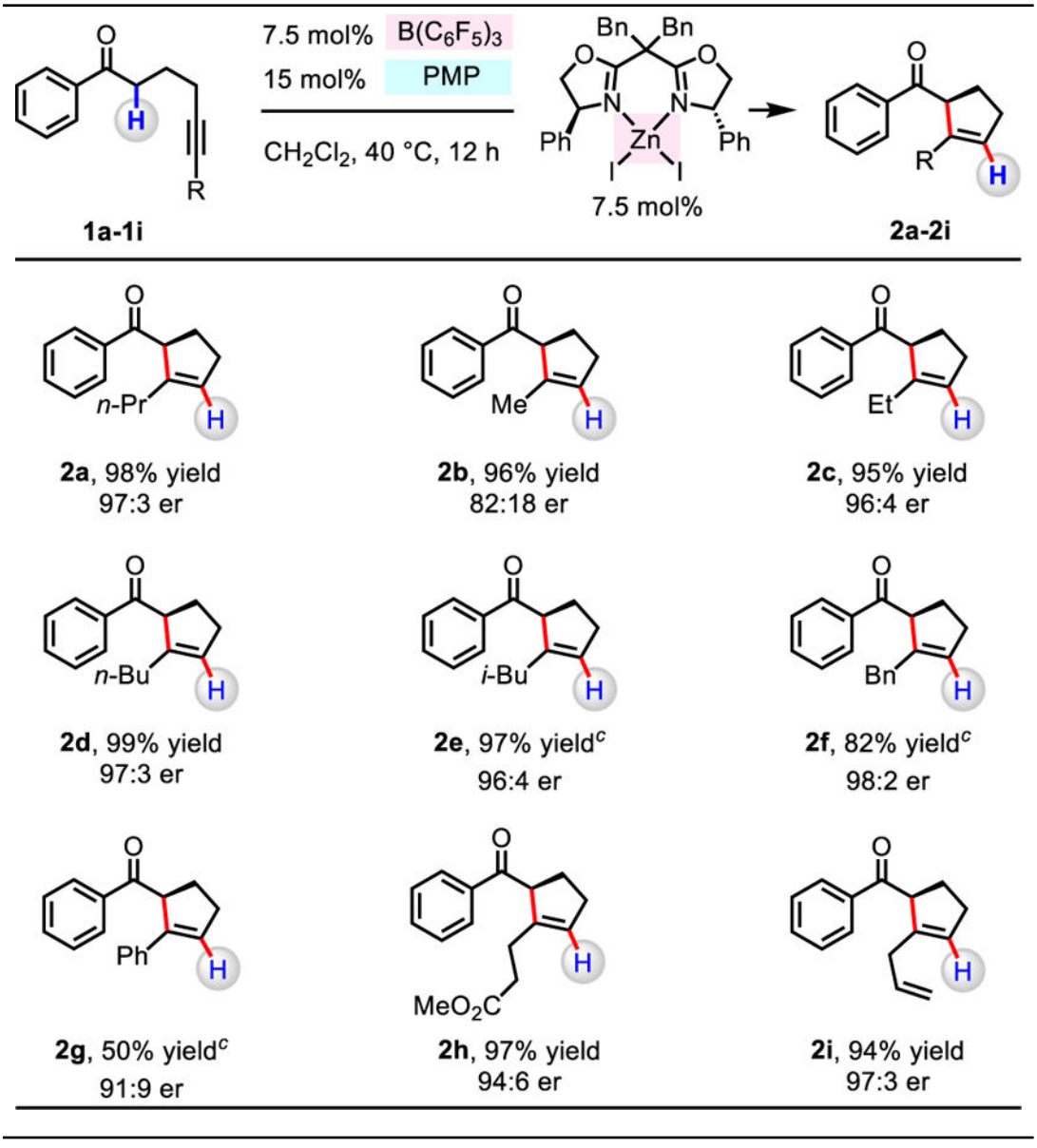
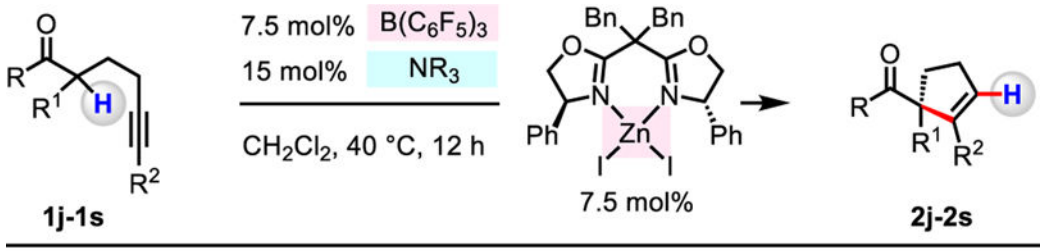
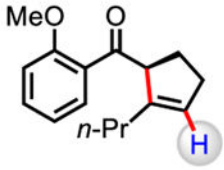


Table 4.

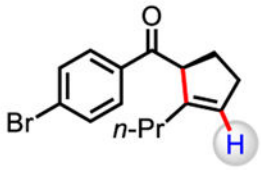
Conia-Ene-Type Reactions with Different Ketones [a,b]

[a]Conditions: Alkynyl ketone (**1j-1l**, **1o-1s**; 0.2 mmol), $B(C_6F_5)_3$ (7.5 mol%), 1,2,2,6,6-pentamethylpiperidine (15 mol%), ZnI_2/**L8** (7.5 mol%), CH_2Cl_2 (1.0 mL), under N_2, 40 °C, 12 h. [b]Yield of isolated and purified product. The er values were determined by HPLC analysis of the purified product. [c]1-Methylpiperidine was used as a Brønsted base catalyst. [d]Alkynyl ketone (**1m**, **1n**; 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1-methylpiperidine (20 mol%), ZnI_2/**L8** (10 mol%), $ClCH_2CH_2Cl$ (1.0 mL), under N_2, 60 °C, 24 h.

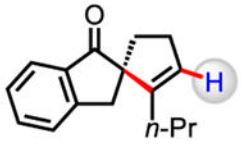




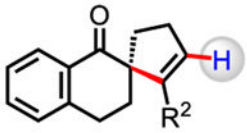
2j, 95% yield
93:7 er



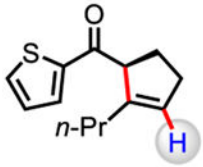
2k, 97% yield
97:3 er



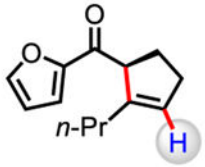
2l, 98% yield[c]
99:1 er



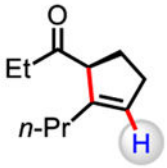
2m (R^2 = *n*-Pr)[c,d]
20% yield, 98:2 er
2n (R^2 = Me)[c,d]
73% yield, 91:9 er



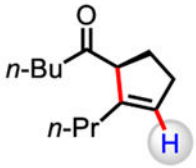
2o, 99% yield
98:2 er



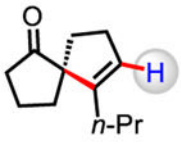
2p, 99% yield
97:3 er



2q, 91% yield
95:5 er



2r, 77% yield
96:4 er



2s, 82% yield[c]
80:20 er