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

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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.

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.

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).

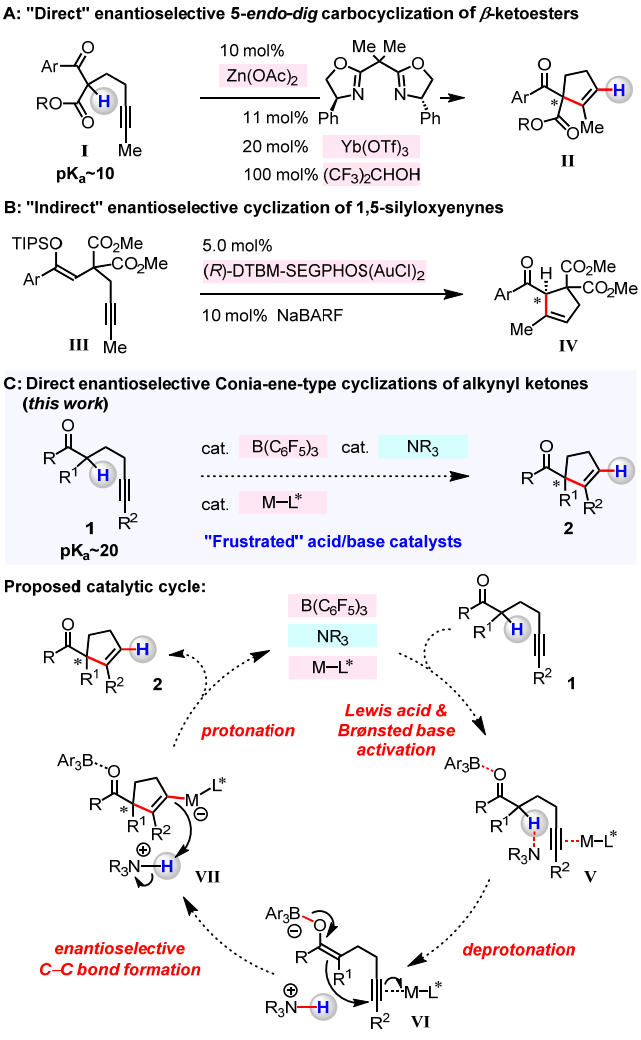


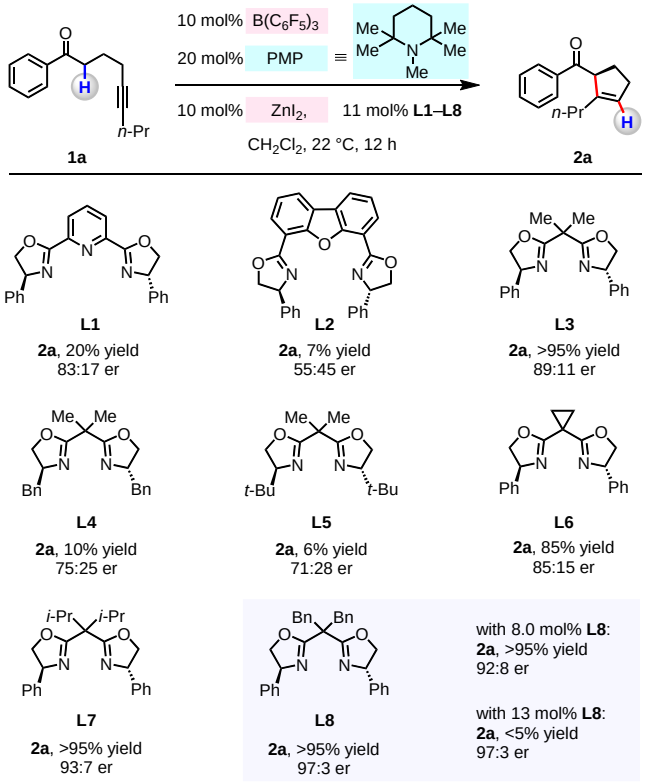
Figure 1. Enantioselective 5-*endo*-*dig* cycloadditions.

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]

Table 1. Evaluation of Bis-oxazoline Ligands [a,b]

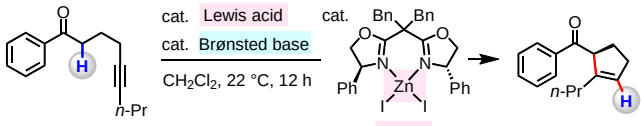


[a] Conditions: 1-phenylnon-5-yn-1-one (**1a**, 0.2 mmol), $B(C_6F_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (20 mol%), ZnI_2 (10 mol%), bis-oxazoline ligand (11 mol%), CH_2Cl_2 (1.0 mL), under N_2, 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product.

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.

Table 2. Evaluation of Reaction Parameters [a,b]



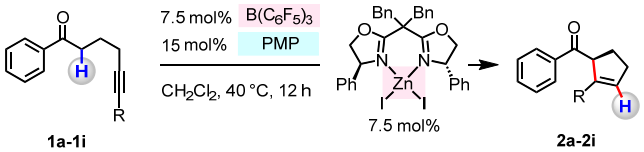
entry	Lewis acid (mol%)	Brønsted base (mol%)	ZnI_2/**L8** (mol%)	yield of **2a** (%)	er
1	$B(C_6F_5)_3$ (10)	NEt_3 (20)	10	>95	97:3
2	$B(C_6F_5)_3$ (10)	DBU (20)	10	0	ND
3	$B(C_6F_5)_3$ (10)	PMP (20)	10	>95	97:3
4	$B(C_6F_5)_3$ (7.5)	PMP (15)	7.5	90	97:3
5[c]	$B(C_6F_5)_3$ (7.5)	PMP (15)	7.5	>95	97:3
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•OEt_2 (5.0)	PMP (10)	5.0	0	ND
11	BPh_3 (5.0)	PMP (10)	5.0	0	ND

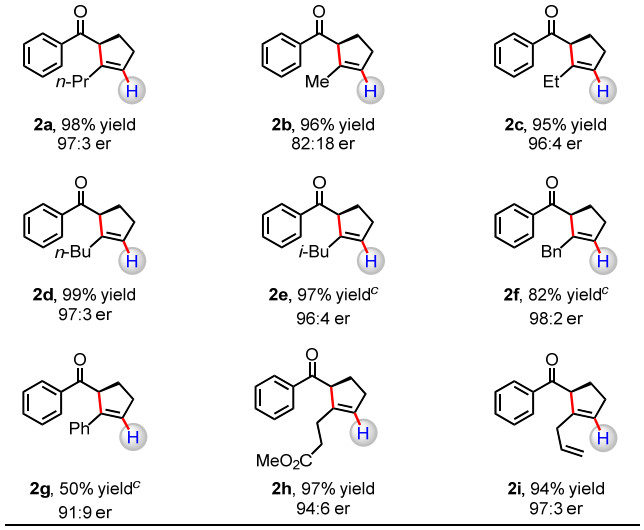
[a] Conditions: 1-phenylnon-5-yn-1-one (**1a**, 0.2 mmol), organoborane, Brønsted base, ZnI_2/**L8** complex, CH_2Cl_2 (1.0 mL), under N_2, 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. The er values were determined by HPLC analysis of the purified product. [c] The reaction mixture was allowed to stir at 40 °C.

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.

Table 3. Conia-Ene-Type Reactions with Different Alkyne Substituents [a,b]



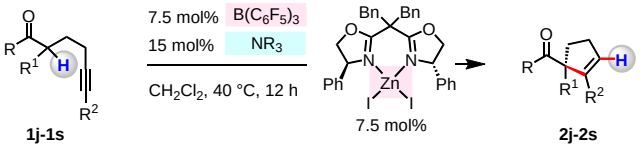


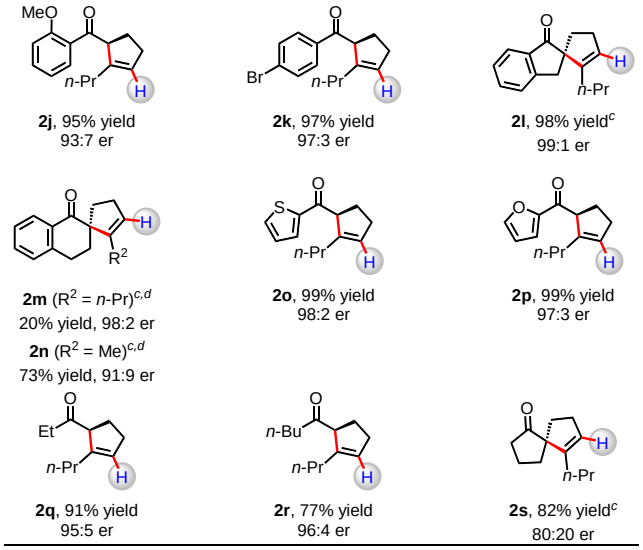
[a] Conditions: Alkynyl ketone (**1a-1d**, **1h**, **1i**; 0.2 mmol), $B(C_6F_5)_3$ (7.5 mol%), 1,2,2,6,6-pentamethylpiperidine (15 mol%), ZnI_2/**L8** (7.5 mol%), CH_2Cl_2 (1.0 mL), under N_2, 40 °C, 12 h. [b] Yield of isolated and purified product. The er values were determined by HPLC analysis of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

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).

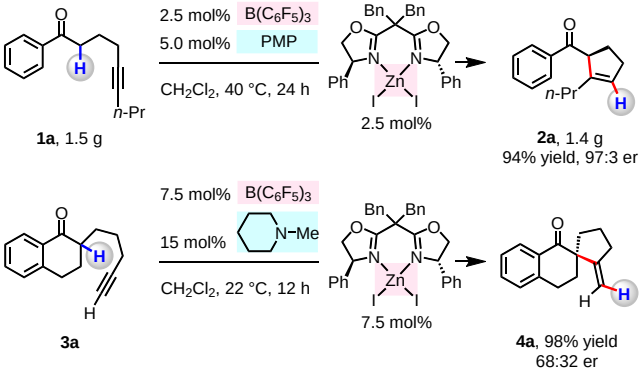
The method is readily scalable. Treatment of 1.5 g (7.0 mmol) of **1a** with 2.5 mol% $B(C_6F_5)_3$, 5.0 mol% PMP and 2.5 mol% ZnI_2/**L8** (CH_2Cl_2, 24 h, 40 °C) afforded **2a** in 94% yield (6.6 mmol, 1.4 g) and 97:3 er (Scheme 1). Moreover, we discovered that cycloaddition of 1-phenylhept-6-yn-1-one (**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.

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.



Scheme 1. Scale-up experiments and 5-*exo*-*dig* cycloaddition of **3a**

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.

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Notes
The authors declare no competing financial interest.

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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.

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

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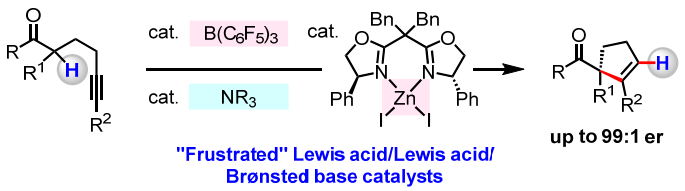
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