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Efficient Access to Chiral Trisubstituted Aziridines *via* Catalytic Enantioselective Aza-Darzens Reactions

Prof. Dr. Barry M. Trost, Dr. Tanguy Saget, and Chao-I (Joey) Hung

Department of Chemistry, Stanford University, Stanford, CA, 94305-5080, USA

Abstract

Herein, we report a Zn-ProPhenol catalyzed aza-Darzens reaction using chlorinated aromatic ketones as nucleophilic partners for the efficient and enantioselective construction of complex trisubstituted aziridines. The α -chloro- β -aminoketone intermediates featuring a chlorinated tetrasubstituted stereocenter can be isolated in high yields and selectivities for further derivatization. Alternatively, they can be directly transformed to the corresponding aziridines in a one pot fashion. Of note, the reaction can be run on gram-scale with low catalyst loading without impacting its efficiency. Moreover, this methodology was extended to α -bromoketones which are scarcely used in enantioselective catalysis because of their sensitivity and lack of accessibility.

Abstract

A Zn-ProPhenol catalysed aza-Darzens reaction using α -chloroketones allows the efficient construction of challenging trisubstituted aziridines with high enantio- and diastereoselectivities (up to 98% ee, >20:1 d.r.). This method also provides an efficient access to complex chlorinated molecules featuring a tertiary stereogenic chloride.

Keywords

aza-Darzens; asymmetric catalysis; Mannich reaction; Zn-ProPhenol; tertiary chloride

Because of their inherent ring strain, aziridines are versatile synthetic intermediates for the synthesis of complex nitrogen-containing molecules.^[1] Moreover, the aziridine motif is also found in many natural products and bioactive compounds.^[2e] In this context, stereoselective methods to access aziridine moieties are particularly relevant. The enantioselective synthesis of aziridines has largely improved over the last two decades.^[2] However, despite these improvements the construction of densely substituted chiral aziridines still represents a synthetic challenge.^[2e] To date, there are only a very limited number of catalytic enantioselective methods to access trisubstituted aziridines.^[2d,3] So far, the two reported

approaches are depicted in Scheme 1: a) reaction of carbenoids with aldimines or ketimines^[4]; b) nitrogen delivery to a Michael-acceptor.^[5] A third approach represented in Scheme 1c has been overlooked, probably because of the lack of stereoselective methods to access the key α -chloro- β -aminoketone intermediates.

Chloroenolates are powerful nucleophiles for the synthesis of stereogenic chlorides adjacent to a carbonyl group, a motif that is commonly found in natural products.^[6] Chloroenolates are also useful coupling partners for aza-Darzens reactions to access aziridine motifs.^[2b] In this context, their use is mostly restricted to diastereoselective reactions using stoichiometric amounts of chiral reagents.^[7] To date, the only reported catalytic enantioselective aza-Darzens reaction is restricted to chloroacetylacetone, which affords aziridines possessing a single stereogenic center (Scheme 2a).^[8]

More generally, the catalytic enantioselective use of chloroenolates is extremely scarce and limited to stabilized enolates derived from chlorinated 1,3-dicarbonyl compounds^[9] or 3-chlorooxindoles.^[10] There are two examples wherein only α -chloroaldehydes can be functionalized *via* an enamine mode of activity using organocatalysis.^[11] The lack of catalytic enantioselective reactions with non-stabilized chloroenolates from α -chloroketones clearly highlights the need for new competent catalytic systems able to perform such reactions. The approach reported herein also highlights the importance of the ability to adjust the catalyst electronically and sterically to tune selectivity/reactivity.

ProPhenol ligands form dinuclear main group metal catalysts when treated with an alkyl metal reagent such as Et₂Zn (Scheme 3).^[12] These chiral bimetallic complexes contain a Lewis acidic and Brønsted basic site and are capable of activating both an electrophile and a nucleophile.^[13]

The Zn-ProPhenol catalytic system is well-suited for direct enantioselective aldol and Mannich-type reactions.^[14] We wondered if this catalytic system could perform enantioselective reactions with non-stabilized chloroenolates to access complex chlorinated molecules that can be converted to trisubstituted aziridines or isolated for alternative usages.

The first hurdle toward the synthesis of trisubstituted aziridines was the development of an unprecedented enantioselective Mannich reaction using substituted α -chloroketones. We initiated our studies by reacting chloroindanone **1a** with imine **2a** in the presence of our standard Zn-ProPhenol catalyst **L1** (Table 1). When the reaction was run in THF, α -chloro- β -aminoketone **3aa** was obtained in a moderate yield and with good selectivities (entry 1). The use of a less coordinating solvent such as diethyl ether resulted in a marked increase of reactivity providing **3aa** quantitatively together with excellent enantio- and diastereoselectivity (entry 2). The reaction proceeds equally well at room temperature (entry 3). However, when this set of conditions was applied to chlorotetralone **1d**, compound **3da** was obtained as a 2.0:1 mixture of diastereoisomers (entry 4). The use of other solvents such as THF or toluene did not improve the diastereomeric ratio (entries 5–6). We then investigated the use of non-C₂-symmetric ProPhenol ligands **L2–L4** which proved to be differential for the enantioselective vinylation of *N*-Boc imines.^[15] **L2** and **L3** did not surpass the standard ProPhenol ligand **L1** (entries 7–8). However, the use of the more

polarized donor-acceptor ligand **L4** significantly improved the diastereoselectivity of the reaction and provided compound **3da** with 96% *ee* (entry 9). This effect was even more pronounced when the reaction was run at 23°C as the diastereomeric ratio could be increased to 6.0:1 (entry 10). Finally, the use of **L4** with substrate **1a** gave **3aa** quantitatively with increased enantioselectivity (entry 11 vs entry 2) and the reaction was complete in less than one hour. The superiority of a non-C₂-symmetric ProPhenol ligand for this reaction highlights the importance of having two differentiated but complementary Zn-centers within the dinuclear complex for an optimal catalytic activity.

We then evaluated the generality of the reaction with a range of chloroketones (Scheme 4). Several chloroindanones were successfully reacted with aromatic *N*-Boc imines (**3ba–3ab**). The relative and absolute configuration of **3ba** was unambiguously established by X-ray crystallographic analysis^[16] and, by analogy, the same configuration was assigned to all compounds **3**. Interestingly, vinyl imines can be successfully used with our standard conditions as shown with **3ac**. Chlorotetralone **1d** and chloro-furanocyclohexanone **1e** afforded **3da** and **3ea** with 3.4:1 and 3.2:1 d.r. respectively. However, in both cases the two diastereoisomers could be easily separated by flash chromatography to afford diastereomerically pure compounds α -chloro- β -amine in good yield. Chloroketones based on the chromanone and benzosuberone skeletons gave the desired product **3fa** and **3ga** in high yields and selectivities. Of note, when **L4** was replaced by **L1**, **3ga** was obtained with much lower enantioselectivity (72% *ee* with **L1** vs 95% *ee* with **L4**) showcasing the superiority of **L4** for this reaction. We are currently working on the use of acyclic chloroketones which represent a limitation for our present catalytic system.^[17]

The catalytic enantioselective use of non-stabilized bromoenolates is extremely scarce.^[18] In this context, we were pleased to extend the scope of the reaction to α -bromoketones using our standard protocol (Scheme 4). Indeed, the 5 and 7 membered bromo-benzocycloalkanones were successfully coupled with both *N*-Boc and *N*-Cbz imines to afford the corresponding α -bromo- β -aminoketones **3ha–3ia** and **3ka** in high yield and perfect selectivities. To the best of our knowledge, the catalytic enantioselective use of bromoketones to access tertiary stereogenic bromides was unprecedented prior to this work.

To showcase the scalability and the practicality of the process, we performed a gram-scale reaction using **1a** and 1.05 equivalent of imine **2a** (Scheme 5). The catalyst loading could be reduced to only 1 mol% without impacting the outcome of the reaction.

With a robust and enantioselective process in hand to access α -chloro- β -aminoketones **3**, we then investigated their transformation to the corresponding aziridines **4** (Scheme 6). After some optimization, two different protocols were developed. Protocol A was Cs₂CO₃ in acetonitrile as solvent. When this protocol was applied to α -chloro- β -aminoketones derived from chloroindanones **1a–c**, the desired aziridines were obtained quantitatively. However, this protocol was not compatible with substrates derived from chlorotetralone **1d**, chloro-furanocyclohexanone **1e**, or chlorochromanones **1f** for which a significant amount of chloride elimination was observed. In this case, switching to protocol B, using NaH in THF, completely prevented elimination to afford the aziridines quantitatively. The relative

configuration of **4da** was confirmed by NOE analysis and is consistent with an aziridine formation *via* an invertive S_N2 displacement of the chloride.^[19]

To further expand the practicality of this reaction, we wished to develop a one-pot process to provide a direct access to trisubstituted aziridines **4** starting from chloroketones **1**. To this end, Cs₂CO₃ or NaH were directly added after completion of the coupling reaction between **1** and **2** (Scheme 7). When Cs₂CO₃ is used as a base, the addition of Florisil® is required to observe conversion to the aziridine. We believe that Florisil® acts as a scavenger of the Zn-ProPhenol catalyst which otherwise inhibits the aziridine formation. We successfully applied this one-pot procedure to the synthesis of aziridines **4aa** and **4af** which were previously obtained with comparable yields and selectivities (*vide supra*). Given the efficiency in which the α-chloro-β-aminoketones of Scheme 3 cyclize to aziridines as shown in Scheme 5, we believe the remaining examples of Scheme 3 obviously will follow in the one-pot process. Thus, to demonstrate the even broader generality of our process, we performed additional examples via the one-pot reaction with a variety of different imines to efficiently access new trisubstituted aziridines **4** without the need to isolate the corresponding α-chloro-β-aminoketone intermediates **3**.

To demonstrate the utility of this method we first attempted to further elaborate some compounds **3** to prove their versatility as synthetic intermediates in processes other than aziridine formation (Scheme 8). Interestingly, when α-chloro-β-aminoketone **3aa** was reacted with 1.5 equivalent of a silver salt in DMF at 60°C, the cyclization mode could be diverted to access oxazolidinone **5** instead of aziridine **4aa**. In our hands, silver nitrate provided a better yield than silver triflate (95% vs 85% yield). In the case of compound **3ha** bearing a tertiary bromide, an intermolecular S_N2 displacement by sodium azide could outcompete the intramolecular formation of aziridine **4aa**. The resulting product **6** corresponds to a formal *syn*-selective diamination of a chalcone derivative with two synthetically differentiable nitrogen atoms. Of note, when this reaction was attempted with **3aa**, the reaction was sluggish and decomposition was observed upon heating. This result highlights the strong synthetic potential of these bromoketone adducts. We then focused on aziridine elaborations. First, **3aa** was deprotected using TFA and the resulting crude mixture was directly subjected to an amide coupling to afford aziridine **7** in 71% overall yield. Additionally, a diastereoselective reduction of ketone **4aa** was developed to afford benzylic alcohol **8** with complete control of the diastereoselectivity.

In summary, we have developed the first catalytic enantioselective aza-Darzens reaction to access complex trisubstituted aziridines starting from readily available chloroketones. Our bimetallic catalytic system is based on a non-C₂-symmetric ProPhenol ligand and allows the enantioselective use of non-stabilized chloroenolates. The reaction proceeds *via* a transient Zn-enolate to afford α-chloro-β-aminoketone intermediates featuring a tertiary stereogenic chloride. These intermediates were isolated in high yields and selectivities and then further elaborated. Alternatively, they could directly afford chiral trisubstituted aziridines in a one pot fashion. Finally, the scope of the reaction was extended to sensitive bromoketones that are scarcely used in enantioselective catalysis. Further work on the enantioselective use of bromo- and chloroenolates is ongoing in our laboratories and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For reviews, see: McCoull W, Davis FA. *Synthesis*. 2000;1347–1365. Sweeney JB. *Chem. Soc. Rev.* 2002; 31:247–258. [PubMed: 12357722] Watson IDG, Yu L, Yudin AK. *Acc. Chem. Res.* 2006; 39:194–206. [PubMed: 16548508] Singh GS, D'hooge M, De Kimpe N. *Chem. Rev.* 2007; 107:2080–2135. [PubMed: 17488062] Schneider C. *Angew. Chem.* 2009; 121:2116–2118. *Angew. Chem. Int. Ed.* 2009, 48, 2082–2084. Stankovic S, D'hooge M, Catak S, Eum H, Waroquier M, Van Speybroeck V, De Kimpe N, Ha H-J. *Chem. Soc. Rev.* 2012; 41:643–665. [PubMed: 21894345] Njardarson JT. *Synlett*. 2013:787–803. Callebaut G, Meiresonne T, De Kimpe N, Mangelinckx S. *Chem. Rev.* 2014; 114:7954–8015. [PubMed: 24773209] Rotstein BH, Zaretsky S, Rai V, Yudin AK. *Chem. Rev.* 2014; 114:8323–8359. [PubMed: 25032909] He Z, Zajdlik A, Yudin AK. *Acc. Chem. Res.* 2014; 47:1029–1040. [PubMed: 24495255] For selected recent examples in total synthesis, see: Menjo Y, Hamajima A, Sasaki N, Hamada Y. *Org. Lett.* 2011; 13:5744–5747. [PubMed: 21966984] Mei R-H, Liu Z-G, Cheng H, Xu L, Wang F-P. *Org. Lett.* 2013; 15:2206–2209. [PubMed: 23587046] Gerstner NG, Adams CS, Grigg RD, Tretbar M, Rigoli JW, Schomaker JM. *Org. Lett.* 2016; 18:284–287. [PubMed: 26741730]
2. For reviews, see: Zhang Y, Lu Z, Wulff WD. *Synlett*. 2009:2715–2739. Sweeney J. *Eur. J. Org. Chem.* 2009:4911–4919. Pellissier H. *Tetrahedron*. 2010; 66:1509–1555. Pellissier H. *Adv. Synth. Catal.* 2014; 356:1899–1935. Degennaro L, Trinchera P, Luisi R. *Chem. Rev.* 2014; 114:7881–7929. [PubMed: 24823261] Zhu Y, Wang Q, Cornwall RG, Shi Y. *Chem. Rev.* 2014; 114:8199–8256. [PubMed: 24785198]
3. For diastereoselective syntheses of trisubstituted aziridines using stoichiometric amounts of chiral reagents, see: Davis FA, Deng J, Zhang Y, Haltiwanger RC. *Tetrahedron*. 2002; 58:7135–7143. Chemla F, Ferreira F. *J. Org. Chem.* 2004; 69:8244–8250. [PubMed: 15549794] Morton D, Pearson D, Field RA, Stockman RA. *Chem. Commun.* 2006:1833–1835. Moragas T, Churcher I, Lewis W, Stockman RA. *Org. Lett.* 2014; 16:6290–6293. [PubMed: 25479333]
4. a) Huang L, Wulff WD. *J. Am. Chem. Soc.* 2011; 133:8892–8895. [PubMed: 21598936] b) Hashimoto T, Nakatsu H, Yamamoto K, Maruoka K. *J. Am. Chem. Soc.* 2011; 133:9730–9733. [PubMed: 21627092]
5. a) De Vincentiis F, Bencivenni G, Pesciaioli F, Mazzanti A, Bartoli G, Galzerano P, Melchiorre P. *Chem. Asian J.* 2010; 5:1652–1656. [PubMed: 20512797] b) Deiana L, Dziedzic P, Zhao G-J, Vesely J, Ibrahim I, Rios R, Sun J, Cordova A. *Chem. Eur. J.* 2011; 17:7904–7917. [PubMed: 21611987] c) Halskov KS, Naicker T, Jensen ME, Jorgensen KA. *Chem. Commun.* 2013; 49:6382–6384. d) Molnar IG, Tanzer E-M, Daniliuc C, Gilmour R. *Chem. Eur. J.* 2014; 20:794–800. [PubMed: 24338989]
6. For a recent review on chlorinated natural products, see: Chung W-J, Vanderwal CD. *Angew. Chem.* 2016; 128:4470–4510. *Angew. Chem. Int. Ed.*, 2016, 55, 4396–4434. For natural products featuring an α -chloroketone motif, see: Soria-Mercado IE, Prieto-Davo A, Jensen PR, Fenical W. *J. Nat. Prod.* 2005; 68:904–910. [PubMed: 15974616] Diaz-Marrero AR, Brito I, de la Rosa JM, Darias J, Cueto M. *Tetrahedron*. 2008; 64:10821–10824. Winter JM, Jansma AL, Handel TM, Moore BS. *Angew. Chem.* 2009; 121:781–784. *Angew. Chem. Int. Ed.* 2009, 48, 767–770. Zhang W, Liu Z, Li S, Lu Y, Chen Y, Zhang H, Zhang G, Zhu Y, Zhang G, Zhang W, Liu J, Zhang C. *J. Nat. Prod.* 2012; 75:1937–1943. [PubMed: 23136829]
7. For the syntheses of chiral disubstituted aziridines *via* aza-Darzens reactions using stoichiometric amounts of chiral reagents, see: Fujisawa T, Hayakawa R, Shimizu M. *Tetrahedron Lett.* 1992;

- 33:7903–7906. Davis FA, Zhou P, Reddy GV. *J. Org. Chem.* 1994; 59:3243–3245. Davis FA, Zhou P, Liang C-H, Reddy RE. *Tetrahedron Asymm.* 1995; 6:1511–1514. Cantrill AA, Hall LD, Jarvis AN, Osborn HMI, Raphy J, Sweeney JB. *Chem. Commun.* 1996:2631–2632. Gennari C, Pain G. *Tetrahedron Lett.* 1996; 37:3747–3750. Sweeney JB, Cantrill AA, McLaren AB, Thobhani S. *Tetrahedron.* 2006; 62:3681–3693. Sweeney JB, Cantrill AA, McLaren AB, Thobhani S. *Tetrahedron.* 2006; 62:3694–3703. Valdez SC, Leighton JL. *J. Am. Chem. Soc.* 2009; 131:14638–14639. [PubMed: 19778019] Sola TM, Churcher I, Lewis W, Stockman RA. *Org. Biomol. Chem.* 2011; 9:5034–5035. [PubMed: 21643589] Colpaert F, Mangelinckx S, De Brabandere S, De Kimpe N. *J. Org. Chem.* 2011; 76:2204–2213. [PubMed: 21381724] Marsini MA, Reeves JT, Desrosiers J-N, Herbage M, Savoie J, Li Z, Fandrick KR, Sader CA, McKibben B, Gao DA, Cui J, Gonnella NC, Lee H, Wei X, Roschangar F, Lu BZ, Senanayake CH. *Org. Lett.* 2015; 17:5614–5617. [PubMed: 26558319]
8. Larson SE, Li G, Rowland GB, Junge D, Huang R, Woodcock HL, Antilla JC. *Org. Lett.* 2011; 13:2188–2191. [PubMed: 21476598]
9. a) Okino T, Hoashi Y, Furukawa T, Xu X, Takemoto Y. *J. Am. Chem. Soc.* 2005; 127:119–125. [PubMed: 15631461] b) Nichols PJ, DeMattei JA, Barnett BR, LeFur NA, Chuang T-H, Piscopio AD, Koch K. *Org. Lett.* 2006; 8:1495–1498. [PubMed: 16562925] c) Andres JM, Manzano R, Pedrosa R. *Chem. Eur. J.* 2008; 14:5116–5119. [PubMed: 18431736] d) Han X, Kwiatkowski J, Xue F, Huang K-W, Lu Y. *Angew. Chem.* 2009; 121:7740–7743. *Angew. Chem. Int. Ed.* 2009, 48, 7604–7607. e) Xuan Y-N, Nie S-Z, Dong L-T, Zhang J-M, Yan M. *Org. Lett.* 2009; 11:1583–1586. [PubMed: 19260703] f) Wang Z, Chen D, Yang Z, Bai S, Liu X, Lin L, Feng X. *Chem. Eur. J.* 2010; 16:10130–10136. [PubMed: 20645351] g) Hatano M, Horibe T, Ishihara K. *Org. Lett.* 2010; 12:3502–3505. [PubMed: 20608665] h) Chauhan P, Chimni SS. *Adv. Synth. Catal.* 2011; 353:3203–3212. i) Liu W-B, Reeves CM, Stoltz BM. *J. Am. Chem. Soc.* 2013; 135:17298–17301. [PubMed: 24160327] j) Hong S, Kim M, Jung M, Ha MW, Lee M, Park Y, Kim M-H, Kim T-S, Lee J, Park H-G. *Org. Biomol. Chem.* 2014; 12:1510–1517. [PubMed: 24448720] k) Bae HY, Song CE. *ACS Catal.* 2015; 5:3613–3619.
10. a) Noole A, Jarving I, Werner F, Lopp M, Malkov A, Kanger T. *Org. Lett.* 2012; 14:4922–4925. [PubMed: 22958139] b) Dou X, Yao W, Zhou B, Lu Y. *Chem. Commun.* 2013; 49:9224–9226.
11. a) Shibatomi K, Yamamoto H. *Angew. Chem.* 2008; 121:7740–7743. *Angew. Chem. Int. Ed.* 2008, 47, 5796–5798. b) Quintard A, Alexakis A. *Chem. Commun.* 2010; 46:4085–4087.
12. For an X-ray structure of a Zn-Prophenol species, see: Xiao Y, Wang Z, Ding K. *Chem. Eur. J.* 2005; 11:3668–3678. [PubMed: 15827981]
13. Trost BM, Ito H. *J. Am. Chem. Soc.* 2000; 122:12003–12004.
14. For a review, see: Trost BM, Bartlett MJ. *Acc. Chem. Res.* 2015; 48:688–701. [PubMed: 25650587] For our recent work on Mannich reactions, see: Trost BM, Hung C-I. *J. Am. Chem. Soc.* 2015; 137:15940–15946. [PubMed: 26630114] Trost BM, Saget T, Lerchen A, Hung C-I. *Angew. Chem.* 2016; 128:791–794. *Angew. Chem. Int. Ed.* 2016, 47, 781–784. Trost BM, Saget T, Hung C-I. *J. Am. Chem. Soc.* 2016; 138:3659–3662. [PubMed: 26952276]
15. Trost BM, Hung C-I, Koester DC, Miller Y. *Org. Lett.* 2015; 17:3778–3781. [PubMed: 26200769]
16. Crystallographic data for **3ba**: CCDC1497490 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
17. When 2-chloropropiophenone was used with the reaction conditions described in Table 1 (entry 9), the corresponding Mannich adduct was obtained in 41% yield and 2.2:1 d.r. The major diastereoisomer was formed with 40% *ee*.
18. a) Kuang Y, Lu Y, Tang Y, Liu X, Lin L, Feng X. *Org. Lett.* 2014; 16:4244–4247. [PubMed: 25090231] b) Morita Y, Yamamoto T, Nagai H, Shimizu Y, Kanai M. *J. Am. Chem. Soc.* 2015; 137:7075–7078. [PubMed: 26011419]
19. See the supporting information for details.

Scheme 1.

Catalytic enantioselective synthesis of trisubstituted aziridines.

a) Antilla and coworkers [3]:

only reported catalytic enantioselective aza-Darzens reaction with chloroenolates

b) This work:

catalytic enantioselective reaction with non-stabilized chloroenolates

Scheme 2.

Aza-Darzens reactions using chloroenolates.

Scheme 3.
Synthesis and structure of a Zn-ProPhenol bimetallic catalyst.

Scheme 4.
Scope of the reaction.

Scheme 5.
Gram-scale reaction with low catalyst loading.

Scheme 6.
Synthesis of trisubstituted aziridines **4** from β -fluoroamines **3**.

Scheme 7.

One-pot synthesis of aziridines **4** from chloroketones **1**.

Scheme 8.
Synthetic applications.

Table 1

Optimization of the reaction conditions.^[a]

entry	1	L	solvent, T	yield ^[b]	d.r. ^[c]	ee ^[d]
1 ^[c]	1a	L1	THF (0.2 M), 40°C	56%	>20:1	93%
2	1a	L1	Et_2O (0.2 M), 40°C	99%	>20:1	95%
3	1a	L1	Et_2O (0.2 M), 23°C	99%	>20:1	97%
4	1d	L1	Et_2O (0.2 M), 40°C	99%	2.0:1	91%
5 ^[f]	1d	L1	THF (1.0 M), 60°C	99%	1.3:1	79%
6	1d	L1	toluene (0.4 M), 40°C	99%	2.0:1	75%
7	1d	L2	Et_2O (0.2 M), 40°C	90%	2.2:1	91%
8	1d	L3	Et_2O (0.2 M), 40°C	99%	1.1:1	91%
9	1d	L4	Et_2O (0.2 M), 40°C	99%	3.4:1	96%
10 ^[g]	1d	L4	Et_2O (0.2 M), 23°C	86%	6.0:1	94%
11 ^[h]	1a	L4	Et_2O (0.2 M), 40°C	99%	>20:1	97%

^[a]Reaction conditions: 0.20 mmol **1**, 0.22 mmol **2**, 5 mol% **L**, 10 mol% Et_2Zn (1M in hexanes), 3 Å molecular sieves (5 mg), in Et_2O (sealed tube) for 14–16 h at the indicated temperature and concentration.

^[b]Isolated yield.

^[c]Determined by $^1\text{H-NMR}$ analysis.

^[d]Determined by HPLC on a chiral stationary phase.

[e] With 20 mol% of **L1** and 40 mol% of Et₂Zn.

[f] With 10 mol% of **L1** and 20 mol% of Et₂Zn.

[g] Reaction time was 28h.

[h] Reaction time was 1h.

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