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Recent Advances in the Catalytic Syntheses of Allenes: A Critical Assessment

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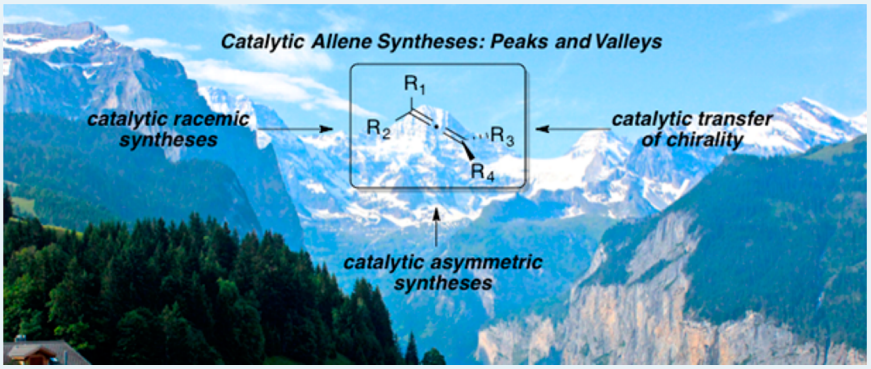

ABSTRACT: The increasing synthetic utility of allenes in organic synthesis combined with their incorporation into a growing list of natural products and active pharmaceutical ingredients has stimulated an intense effort recently to identify efficient catalytic methods for their synthesis. In addition, as the only common functional group in organic chemistry that possesses axial chirality, efforts to discover new asymmetric catalysts for the enantioselective synthesis of axially chiral allenes has intensified as these substrates become more ubiquitous as chiral building blocks for downstream asymmetric methodologies. Nonetheless, despite this intensive effort, the ability to access racemic or chiral allenes from readily available starting materials using catalytic processes has yet to meet the demand of their expanding applications. The focus of this Perspective is to provide a critical assessment on the most recent developments in the field of catalytic syntheses of allenes (2011−2013) highlighting both the advantages and limitations associated with current approaches with a future outlook on the unmet synthetic need that still persists.

KEYWORDS: *allenes, catalysis, axial chirality, asymmetric synthesis, chirality transfer*

1. INTRODUCTION

Allenes enjoy a unique niche as a functional group in organic chemistry. Their orthogonal cumulative π-systems provide complementary yet, in some cases, distinct reactivity compared with their alkene and alkyne cousins. Moreover, their ability to possess axial chirality sets them apart from all other functional groups. Not surprisingly, the exclusive architecture of allenes has resulted in their incorporation in new methodologies as both racemic and chiral building blocks.[1,2] Perhaps more importantly, their occurrence in an ever-growing list of natural products (many of which are chiral), several marketed drugs (Enprostil, Fenprostalene, and Prostalene) and molecular materials solidify their prominence beyond simple reaction chemistry.[3,4] Nonetheless, despite their newfound popularity, the development of *catalytic* methodologies that can access allenes (either in racemic or in enantiomerically enriched form) from readily available starting materials has dramatically lagged behind their utilization in organic synthesis. The argument can be made that the shortage of robust and efficient catalytic methodologies that produce diverse arrays of allenes has stymied the full reaction potential and limited the industrial application of the only common functional group in organic chemistry that possess axial chirality. As a testimony to this fact, at the time this Perspective was written, not a single enantiomerically enriched chiral allene was commercially available.[5]

Several excellent reviews on the synthesis and utility of allenes have appeared lately.[6] Thus, this Perspective will focus on the most recent developments during the past three years (2011−2013), during which we have witnessed significant advances in the catalytic syntheses of allenes in the history of the field. These include several catalytic racemic syntheses of allenes with significant potential for further development into catalytic asymmetric syntheses of chiral allenes. In addition, various catalytic asymmetric syntheses of chiral allenes involving chiral substrates (stoichiometric chirality transfer) have also recently appeared. A brief discussion on these methodologies is included; however, the major focus presented here is toward recent discoveries involving catalytic asymmetric syntheses of chiral allenes from prochiral substrates using substoichiometric chiral sources to control axial chirality. This is an area that we feel is still in its infancy in many respects.

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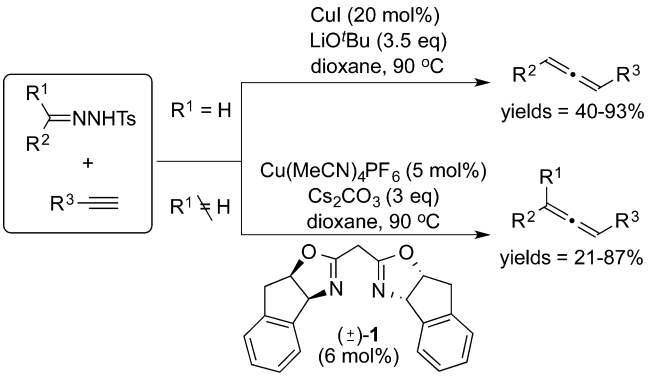
Finally, a critical assessment of the limitations of currently available methodologies will be provided in an effort to highlight the unmet synthetic need that still persists today, despite these recent advancements.

1. RECENT NOTABLE ADVANCES IN THE CATALYTIC RACEMIC SYNTHESES OF ALLENES

Historically, the large majority of racemic allene syntheses rely on the use of acetylenic-based starting materials to access substituted allenes. Current efforts are no exception to this trend. For example, elegant work recently reported by Wang on the coupling of *N*-tosylhydrazones and terminal alkynes via Cu(I) catalysis provides a very convenient and modular racemic approach to 1,3-disubstituted and trisubstituted allenes (Scheme 1).[7] Two separate reaction conditions were reported

Scheme 1. Cu(I)-Catalyzed Racemic Coupling of *N*-Tosylhydrazones and Terminal Alkynes to Substituted Allenes



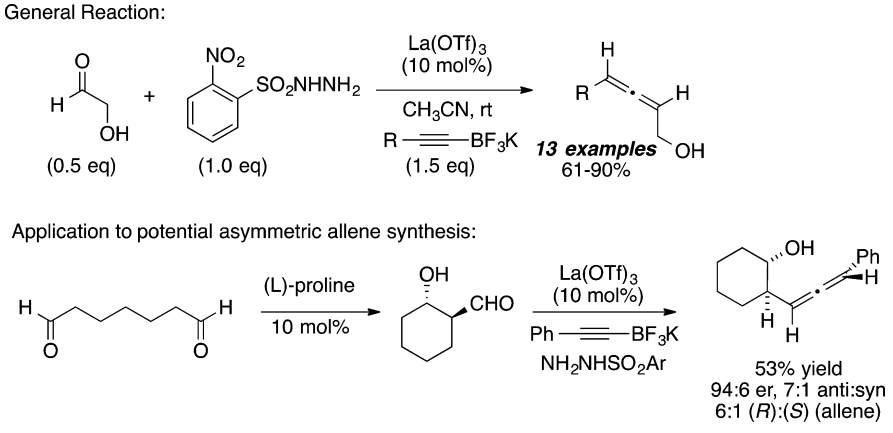
on the basis of whether the *N*-tosylhydrazone was derived from an aldehyde or ketone to gain access to either the 1,3-disubstituted or trisubstituted allene, respectively. Overall, the scope with respect to the carbonyl derivative and terminal alkyne was quite general and the reaction protocol is relatively easy to perform and scalable, making it one of the more attractive racemic syntheses available for 1,3-disubstituted and trisubstituted allenes to date. It is interesting to note that reactions involving ketone-derived *N*-tosylhydrazones required the use of bisoxazoline ligand **1** (racemic), suggesting the possibility of chiral induction through the use of chiral ligands. No subsequent report, however, has appeared on an asymmetric version of this reaction.

The Thomson group recently reported a catalytic racemic route to substituted allenes that also uses the combination of hydrazones and terminal acetylenes (Scheme 2).[8] Here, the terminal acetylene is brought in as a potassium trifluoroborate salt that is required for the Petasis-type coupling reaction that ultimately extrudes nitrogen and sulfinic acid to produce the allene as a "traceless" approach. A survey of various Lewis acids identified La(OTf)$_3$ (10 mol %) as the preferred catalyst that most likely promotes the formation of the hydrazone and the subsequent addition of the alkynyl borane to produce the intermediate propargyl hydrazide. The reaction conditions are surprisingly mild, occurring at room temperature while the reported isolated yields of the corresponding allenyl alcohol products are generally high (61−90%). Although the methodology appears limited to the synthesis of 1,3-disubstituted allenes, they were able to obtain useful levels of diastereoselectivity starting from chiral substrates that may ultimately pave the way for a catalytic enantioselective version of this novel transformation.

The Fox group also recently reported on the Cu-catalyzed coupling of terminal alkynes and substituted α-diazoesters to provide 2,4-disubstituted allenoates.[9] Key to the success of this reaction was the realization that small amounts of base (K_2CO_3, in this case) were necessary to isomerize the initially formed alkynoate to the corresponding allenoate. The optimized reaction conditions employ the use of 5 mol % Cu(II)-(trifluoroacetylacetonate)$_2$, 5 mol % 3,6-di(2-pyridyl)-*s*-tetrazine, and 1 equiv of K_2CO_3 in dichloroethane at 45 °C (Scheme 3). Under these conditions, a range of α-aryl diazoacetates were coupled to several aliphatic alkynes to provide the substituted allenoates in good yields (44−71%). Furthermore, using a slightly modified procedure, they were able to successfully couple both ethyl diazopropionate and ethyl diazobutanoate, as well. The simplicity of this procedure combined with the availability of both coupling partners makes this a highly attractive catalytic approach to racemic substituted allenoates.

Isomerization of internal alkynes has also proven to be a successful strategy for the construction of the allene architecture. An interesting twist on this concept was recently reported using a thiazolium-catalyzed redox isomerization of

Scheme 2. Lewis Acid-Catalyzed Coupling of Alkynyl Trifluoroborates Salts and Sulfonylhydrazones En Route to Racemic Allenyl Alcohols



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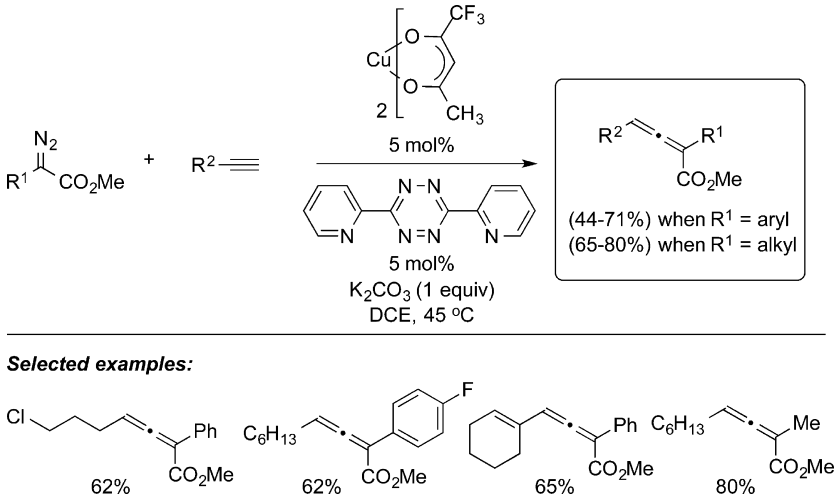
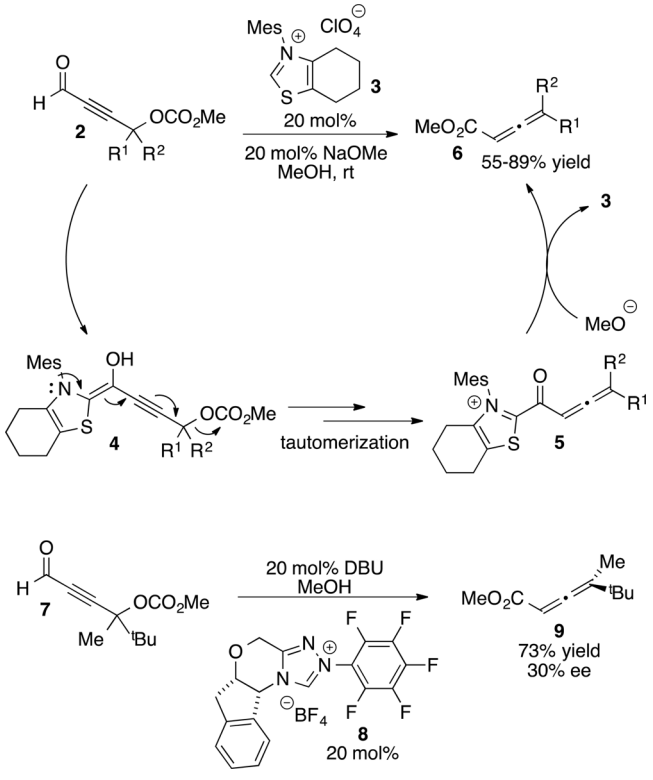
Scheme 3. Cu(II)-Catalyzed Coupling of Substituted α-Diazoesters and Alkynes En Route to Substituted Allenoates



acetylenic aldehydes.[10] By conveniently placing a leaving group at the propargylic position in the starting alkynals **2**, nucleophilic attack by the preferred catalyst **3** induces an internal decomposition/isomerization of the initial Breslow-like intermediate **4** to the acylated catalyst **5**. Subsequent nucleophilic attack of solvent regenerates the catalyst and produces the corresponding allenoate **6** (Scheme 4). The simplicity of this approach is only counterbalanced by the requisite synthesis of the starting alkynals and the difficulty in separating the corresponding isomeric alkynoates when either R^1 or R^2 is hydrogen. Despite these hurdles, the initial scope presented is impressive, and the development of a potential catalytic asymmetric approach seems viable. For example, using

Scheme 4. Thiazolium-Catalyzed Internal Redox Isomerization of Alkynals to Allenoates



Rovis' chiral triazolium catalyst **8**,[11] chiral allenoate **9** was obtained in moderate enantioselectivity and yield.

In addition to alkynes, 1,3-dienes have also proved to be viable substrates for the catalytic synthesis of allenes, as originally pioneered by the work of Hayashi.[12] Two recent publications have extended the successful use of 1,3-dienes in allene synthesis via Pd catalysis to externally add nucleophiles to activated metal complexes. The first report utilizes doubly activated 3-bromopenta-2,4-dienyl acetate (**10**), which is capable of generating two successive Pd π-allyl complexes, allowing for the construction of C_2-symmetric allenes (Scheme 5).[13] A wide range of soft carbon-based nucleophiles were successfully employed in this methodology. In addition, a single example of a catalytic asymmetric chiral allene synthesis was demonstrated using (*R*)-segphos to generate chiral allene **11** in moderate yield and high enantioselectivity, consistent with previous results from the Hayashi group. The second report from the Moberg group involves the Pd-catalyzed cross-coupling between 1,3-dienyl-2-silanols and aryl iodides to generate trisubstituted and, more importantly, tetrasubstituted allenes (Scheme 6).[14] While the preparation of the requisite starting materials remains a limitation to the full exploitation of this approach, the ability to synthesize tetrasubstituted allenes stands as one of the only few methods that can stake this claim.

2. RECENT ADVANCEMENTS IN THE CATALYTIC SYNTHESES OF CHIRAL ALLENES VIA STOICHIOMETRIC CHIRALITY TRANSFER

Without question, some of the most successful and useful asymmetric syntheses of chiral allenes involve the stoichiometric chirality transfer from enantioenriched starting materials. The overwhelming majority of these methodologies have utilized chiral propargylic substrates given the multitude of catalytic asymmetric methodologies available to synthesize these chiral building blocks.[15] Recent developments in this area continue to exploit enantioenriched chiral propargylic substrates to access chiral allenes; however, the focus has shifted to identifying catalytic methods to effect either isomerizations or nucleophilic additions to chiral propargylic substrates as a more atom economical approach to chiral allenes. We have chosen to highlight a few of these recent advances here with a focus on those that use catalytic amounts of transition metals to access

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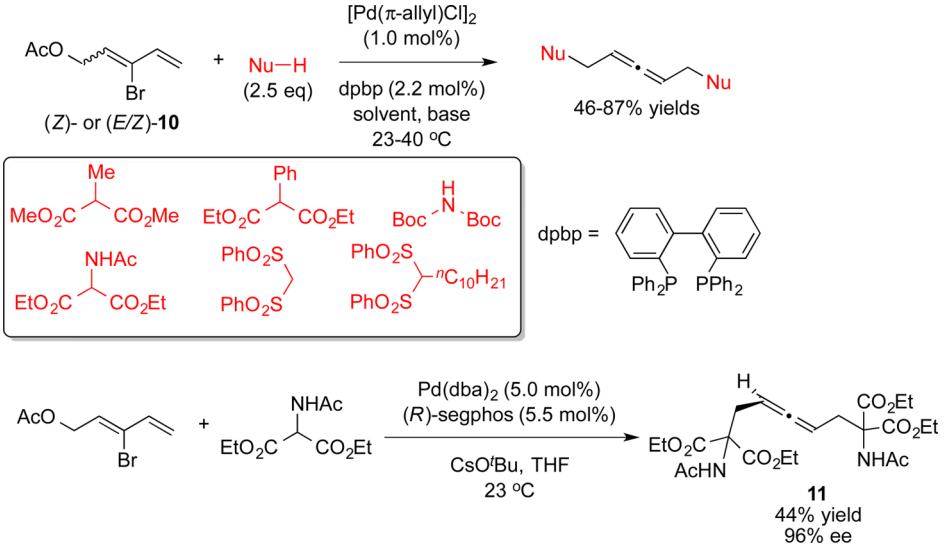
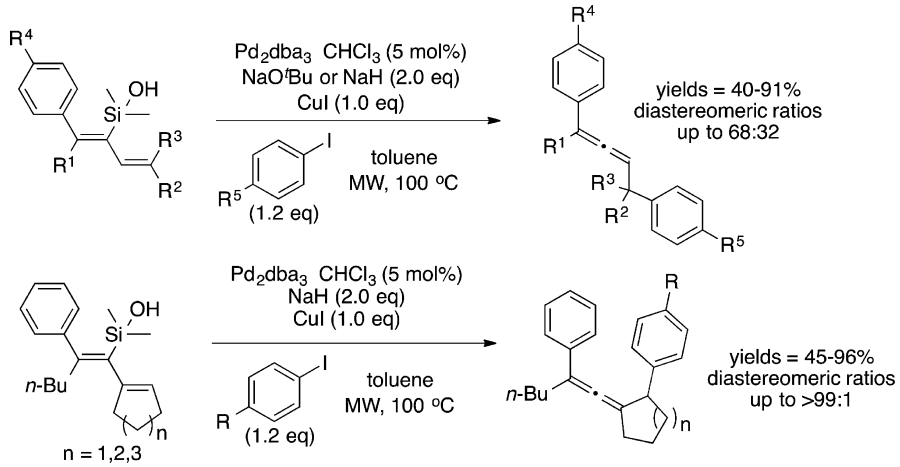
Scheme 5. C_2-Symmetric Allenes from the Pd-Catalyzed Double-Nucleophilic Addition to 3-Bromopenta-2,4-dienyl Acetate



Scheme 6. Pd-Catalyzed Cross-Coupling of 1,3-Dienyl-2-silanols with Aryl Iodides To Access Trisubstituted and Tetrasubstituted Allenes



chiral allenes from enantioenriched chiral propargylic substrates (either discretely or generated in situ).

Several recent publications from both the Ma and Periasamy research groups have continued to refine the use of stoichiometric chiral amines and substoichiometric amounts of zinc(II) or Cu(I) salts as an enantioselective approach to simple disubstituted chiral allenes using terminal alkynes and aldehydes as starting materials.[16] The most utilized chiral amine in this work is (*S*)-α,α-diphenylprolinol **12**, although others have also been employed, including chiral amines **13** and **14** (Scheme 7). In general, the methodology developed by both groups parallel and, in some cases, overlap each other; however, there has also been some discrepancy in the results between the two groups that has been openly discussed.[16] Although these reactions require high catalyst loadings (most require 50−75 mol % of catalyst or cocatalyst), the broad scope and high enantioselectivities observed in the resulting allenes compensate for this drawback. Furthermore, the extensive commercial availability of both aldehydes and terminal alkynes provides an avenue of practicality that will be appreciated by most synthetic chemists.

Enantioenriched propargylic phosphates have also been recently used as stoichiometric chiral building blocks to access axially chiral allenes. Three almost simultaneous publications appeared that highlighted the Cu(I)-catalyzed cross-coupling of chiral propargylic phosphates with alkyl and aryl boranes (Scheme 8).[17] The intermediacy of an organocopper species was supported by both independent studies and is consistent with the previous pioneering work of Crabbé.[18] There are subtle differences between the two reported methodologies, but in general, the reaction conditions are remarkably similar, and chirality transfer from the propargyl phosphates to the chiral allenes is very high in each case. The modular approach here that combines the broad accessibility of the starting propargyl phosphates with general availability of alkyl or aryl boranes makes this one of the most promising approaches to trisubstituted chiral allenes.

3. RECENT ADVANCEMENTS IN THE CATALYTIC ASYMMETRIC SYNTHESES OF CHIRAL ALLENES

The discovery and development of new catalytic asymmetric methodologies remains a fundamental challenge and priority in organic synthesis. Despite the incredible repertoire of chiral

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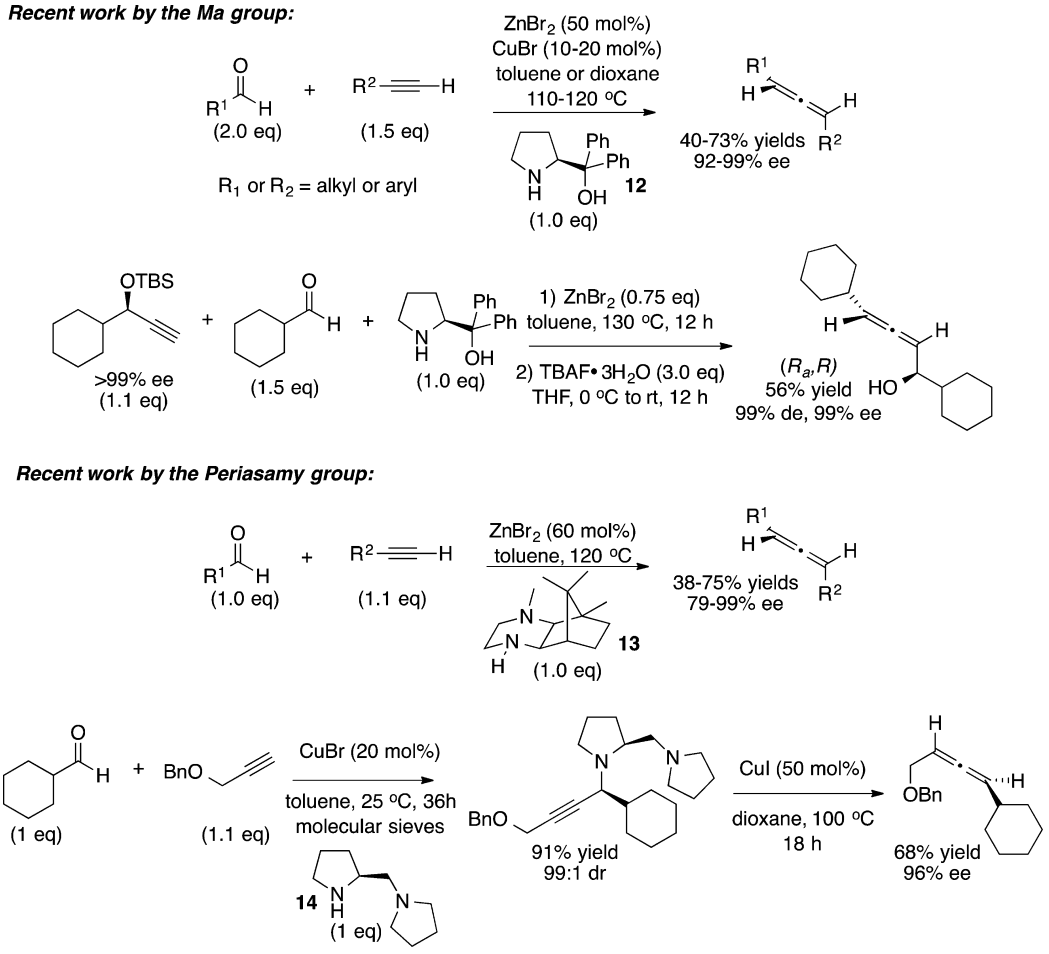
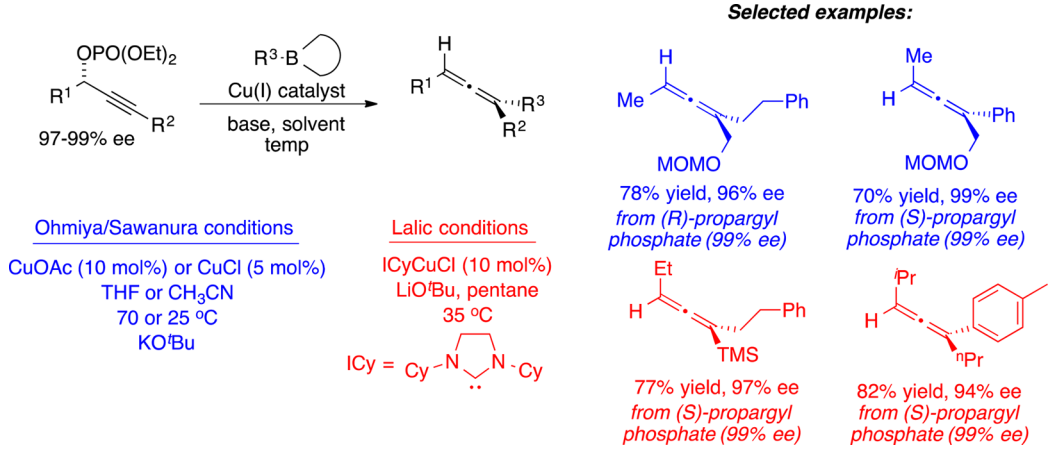
Scheme 7. Recent Work by the Ma and Periasamy Groups Using Stoichiometric Chiral Amines and Catalytic Metals To Access Chiral Allenes



Scheme 8. Cu(I)-Catalyzed Asymmetric Synthesis of Trisubstituted Allenes from Enantioenriched Propargyl Phosphates and Alkyl or Aryl Boron Reagents



catalysts available (either metal-based or carbon-based) and the increasing ability to rationally design new ones, critical gaps still remain in several areas of asymmetric synthesis, most notably in the catalytic construction of axial chirality. Nowhere is this gap more obvious than in the synthesis of chiral allenes. The scope of current methodologies overlap significantly and many share a common mechanistic pathway (i.e., nucleophilic addition to chiral Pd-π-allyl complexes) that limits the structural variability in the allenes obtainable. However, the past three years (2011–2013) have seen significant developments in new methodologies for the catalytic asymmetric syntheses of chiral allenes. In fact, several of these offer completely new mechanistic pathways that may offer opportunities for future exploitation and optimization as these methodologies mature. The selected methodologies highlighted here were chosen on the basis of

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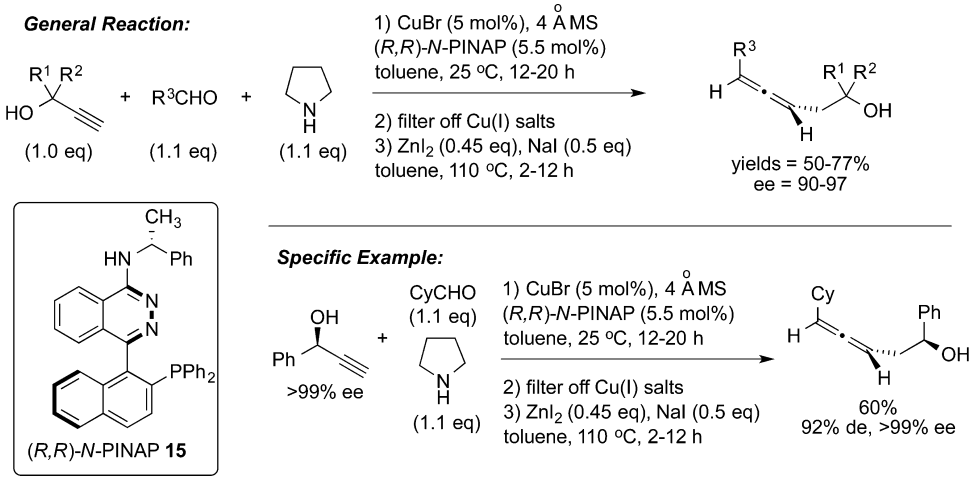
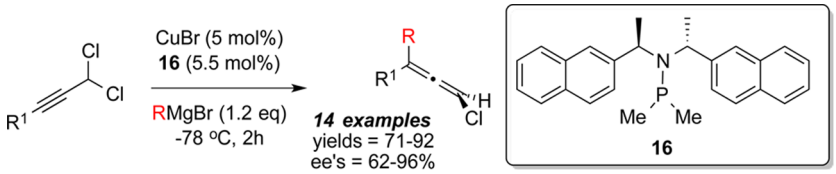
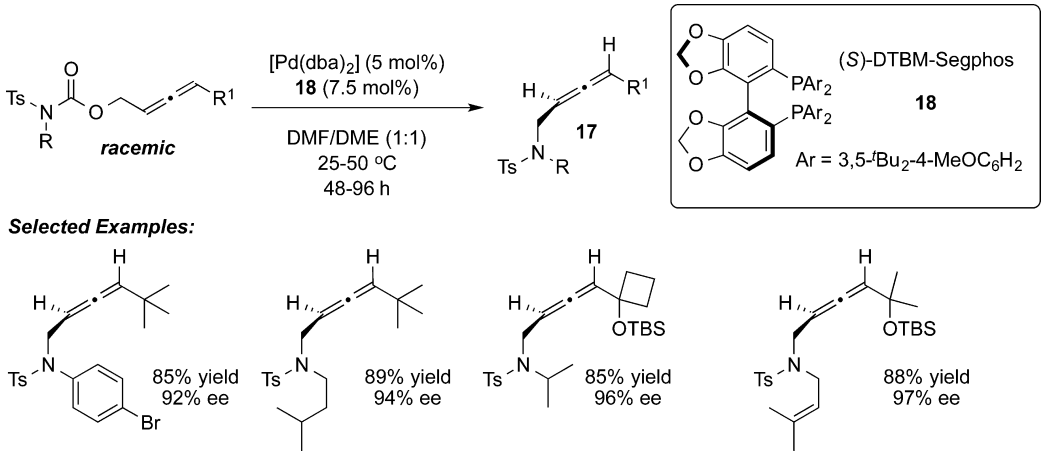
Scheme 9. Catalytic Asymmetric Synthesis of 1,3-Disubstituted Chiral Allenes from Terminal Alkynes and Aldehydes



Scheme 10. Catalytic Asymmetric Synthesis Chloroallenes from Propargyl Dichlorides



Scheme 11. Dynamic Kinetic Asymmetric Decarboxylative Amination of Racemic Allenyl *N*-Tosylcarbamates via Pd Catalysis



their ability to access a broad scope of chiral allenes using only substoichiometric amounts of chiral reagents.

In 2012, the Ma group published a report on the catalytic asymmetric synthesis of chiral allenes that exploited their previous experience in the amine-promoted condensation of terminal alkynes and aldehydes.[19] They envisioned that if the first step of the reaction could be rendered asymmetric (generation of the propargyl amine), then chirality transfer could occur during the subsequent Zn-mediated elimination of the amine to the chiral allene. Thus, the combination of catalytic amounts of CuBr (5 mol %) and (*R*,*R*)-*N*-PINAP (**15**)[20] (5.5 mol %) followed by Zn-mediated elimination/isomerization yielded the corresponding 1,3-disubstituted allenes in good yields and high enantioselectivities (Scheme 9). Some subtleties and limitations, however, are worthy of mention. First, for efficient chirality transfer, the Cu(I) salts from the first step must first be filtered away from the reaction. Second, terminal propargyl alcohols are required to achieve high enantioselectivities, thus placing a limit on the scope of this methodology. Nonetheless, the extrapolation of this approach to optically active propargyl alcohols provides a highly diastereoselective and enantioselective synthesis of the corresponding chiral allenes (Scheme 9).

Methodologies that can access halogenated allenes have significant value not only for their synthetic potential but also for the fact that several allene-containing natural products are halogenated allenes.[3] The recent work from the Alexakis group has provided one of the few catalytic asymmetric approaches to chiral chloroallenes (Scheme 10).[21] A very practical and simple protocol was developed that utilizes prochiral propargyl dichlorides and Grignard reagents originally exploited by Knochel in his own synthesis of racemic chloroallenes.[22] Key to achieving high enantioselectivities was the development of new SimplePhos derivatives, such as ligand **16**, during the

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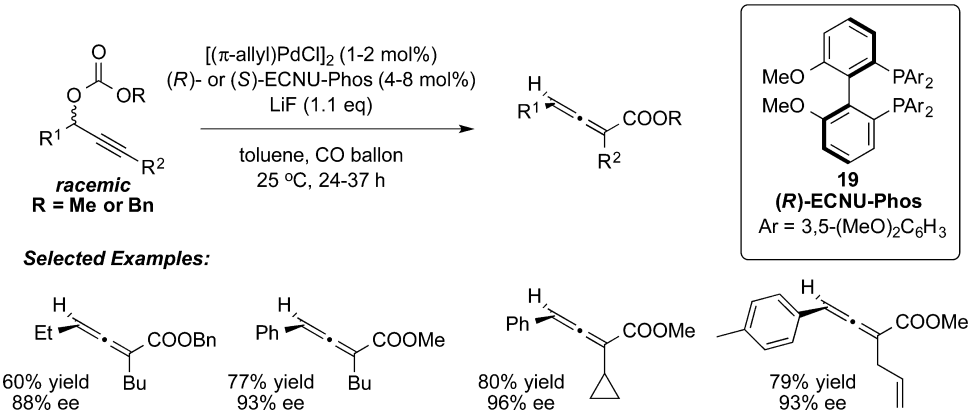
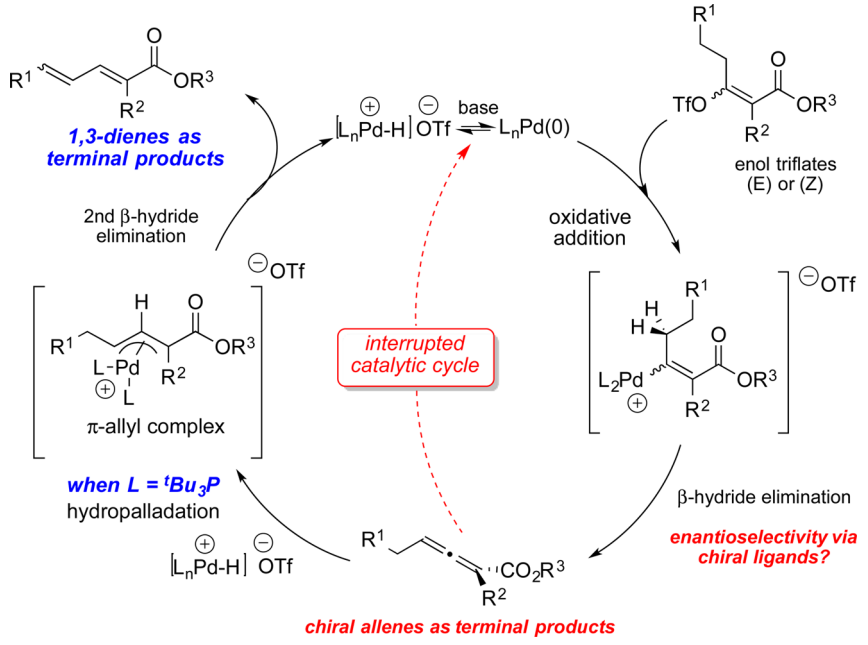
Scheme 12. Dynamic Kinetic Asymmetric Carbonylation of Racemic Propargylic Carbonates via Pd Catalysis



Scheme 13. Pd-Catalyzed Divergent Pathways to 1,3-Dienes or Allenes from Stereodefined Enol Triflates



course of this work. Although the compatibility of the highly basic and nucleophilic Grignard reagents may limit functional group tolerability, the novelty of the chiral chloroallene products is a welcome addition to the growing repertoire of axially chiral allenes.

Another successful strategy that has been utilized to access enantioenriched chiral allenes is through the asymmetric addition of nucleophiles to equilibrating chiral diastereomeric vinyl-allyl Pd(II) complexes.[12,23] Two very recent reports from the Ma group have exploited this concept to access both chiral 1,3-disubstituted and trisubstituted allenes. In the first report,[24] chiral 1,3-disubstituted allenic amines **17** are obtained in high enantiomeric excess through a dynamic kinetic asymmetric decarboxylative amination of racemic allenyl *N*-tosylcarbamates via Pd-catalysis (Scheme 11). Systematic screening of several chiral aryl phosphines revealed Segphos-based ligands were most effective with (*S*)-DTBM-Segphos (**18**), providing the highest enantioselectivities. The reaction conditions are quite mild, and tolerance for various functional groups, including aryl bromides, alkenes, alkynes, and protected alcohols, is demonstrated. The limitations here include prolonged reaction times (up to 4 days) and the requirement for the racemic allenyl *N*-tosylcarbamate starting materials that are nontrivial to access.

The second report from the Ma group entails the catalytic dynamic kinetic asymmetric carbonylation of racemic propargylic carbonates to access enantioenriched chiral trisubstituted allenoates (Scheme 12).[25] Once again, a systematic approach to optimize the chiral ligand proved very effective to ultimately identify ECNU-Phos (**19**) as a newly designed ligand for this process. Reaction conditions are simple, requiring only 1 atm of CO pressure at room temperature with relatively low catalyst loadings (2−4 mol % Pd). In addition, the substrate scope is impressive and the synthetic utility of the corresponding chiral allenoates ensures the broad utility of this approach in asymmetric synthesis.

Our own work in this area was predicated on our ability to exploit stereodefined enol triflates as pluripotent substrates in various catalytic processes. In previous studies, we had identified a Pd-catalyzed elimination/isomerization of enol triflates to 1,3-dienes.[26] The key step involved a facile β-hydride elimination from a cationic vinyl Pd(II)-complex to initially generate an allene intermediate that underwent subsequent hydropalladation, followed by a second β-hydride elimination,

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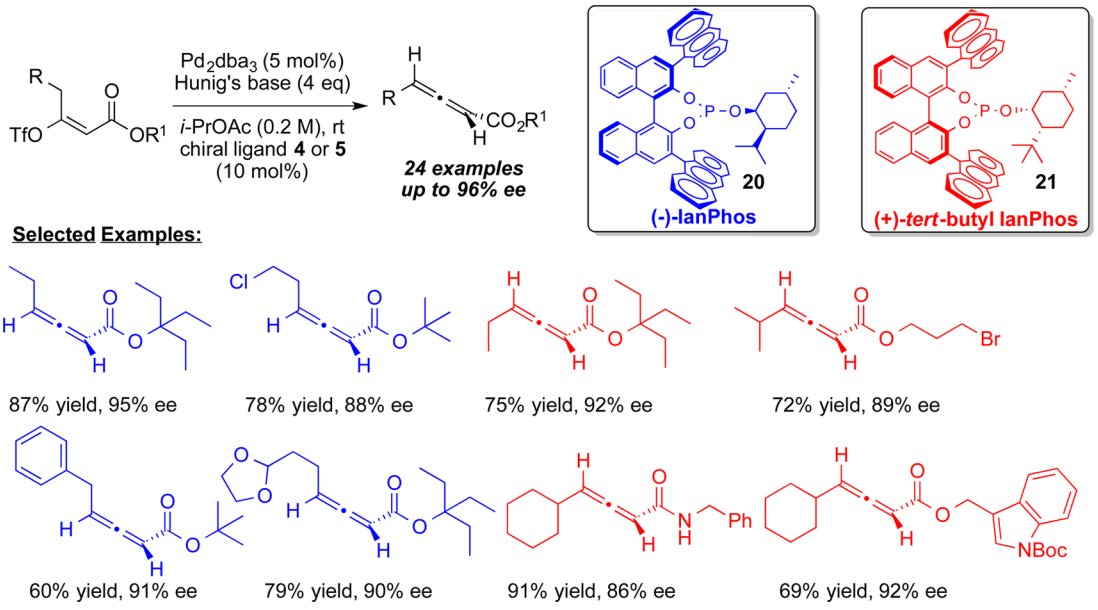
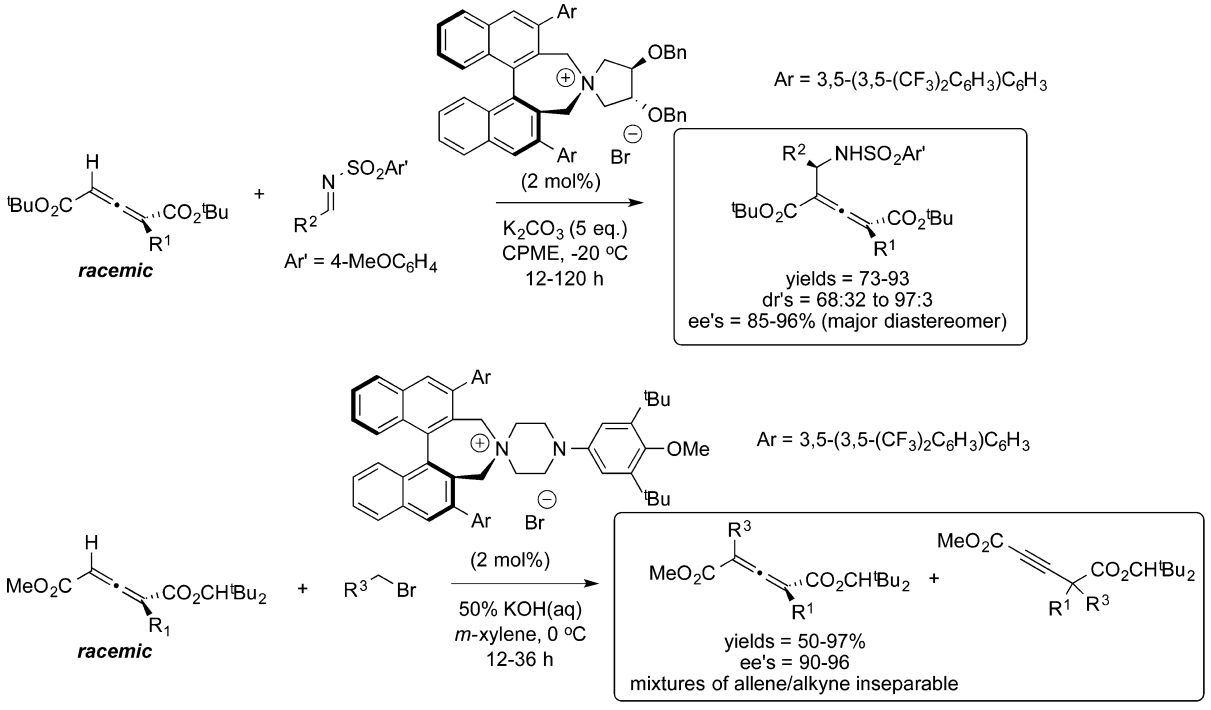
Scheme 14. Pd-Catalyzed Asymmetric β-Hydride Elimination En Route to Chiral 1,3-Disubstituted Allenes



Scheme 15. Catalytic Synthesis of Chiral Tetrasubstituted Allenes via Chiral Phase Transfer Catalysis



to provide the 1,3-diene as the final product (Scheme 13). We envisioned the ability to interrupt this catalytic cycle by rapid turnover of the resulting initial Pd-hydride that would provide the allene as the terminal product in these reactions. Furthermore, we believed a completely novel approach to chiral 1,3-disubstituted allenes was feasible via an asymmetric β-hydride elimination from the cationic vinyl Pd(II) complex by the incorporation of chiral ligands.

Key to the success of this approach was the realization early on during our initial screens that the allenes were, in fact, being generated in high enantioselectivities initially, but racemization during the course of the reaction with prototypical chiral phosphine ligands was reducing our selectivities. Gratifyingly, a simple switch to chiral phosphite ligands retained reactivity but drastically reduced the amount of racemization as the reaction proceeded. Through extensive optimization, we ultimately designed our own novel class of chiral phosphite ligands (−)-IanPhos (**20**) and (+)-*tert*-butyl IanPhos (**21**) (Scheme 14).[27] These ligands solved several problems during the development of this methodology, including rapid turnover of the Pd-hydride intermediate, induced high asymmetric induction during the β-hydride elimination step, and minimized racemization of the allene during the course of the reaction. The methodology displays broad generality with respect to functional group tolerance that includes alkyl and aryl halides, amides, terminal olefins, and acetals.

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Nonetheless, our methodology is not without limitations. First, at this stage of development, we are unable to successfully employ (*Z*)-enol triflates in this reaction. We believe that their lack of reactivity is due to the attenuated agostic interaction with the β-hydrogens via internal chelation of the adjacent carbonyl group in the cationic vinyl Pd(II) complex. Second, fully substituted (*E*)-enol triflates that would give rise to chiral trisubstituted allenoates suffer from poor conversion and low enantioselectivities. Nonetheless, the relative ease of accessing (*E*)-enol triflates[28] combined with the readily scalable synthesis of both ligands (−)-IanPhos (**20**) and (+)-*tert*-butyl IanPhos (**21**) should provide the synthetic community a robust approach to enantioenriched 1,3-disubstituted allenoates.

One of the most demanding challenges in the catalytic asymmetric synthesis of chiral allenes is the ability to access tetrasubstituted allenes. The recent work from the Maruoka group has done just that and represents one of the most significant advances in the field of chiral allene synthesis.[29] Their approach involves the generation of a chiral ammonium cumulenolate via a tight ion pair with various chiral ammonium phase transfer catalysts (Scheme 15). The cumulenolate can be alkylated via a Mannich-type reaction with tosyl imines or via a simple alkylation with alkyl halides, providing chiral tetrasubstituted allenes in high diastereoselectivites or enantioselectivities. The only limitations are that the starting materials are allenoates themselves, and access to the elaborated chiral phase transfer catalysts may prove laborious. Finally, the generation of inseparable mixtures of allenes and alkynoates during the alkylation with simple alkyl halides also instills a potential synthetic limitation to accessing pure chiral allenes. Despite these drawbacks, however, the methodology is unmatched in its ability to provide chiral tetrasubstituted allenes.

4. OUTLOOK AND PERSPECTIVES

The past 3 years (2011−2013) have witnessed some of the most significant advances in the catalytic syntheses of both racemic and chiral allenes. In particular, the recent developments of novel catalytic asymmetric approaches to chiral allenes using substoichiometric sources of chiral information have dramatically increased the ability to access these powerful chiral building blocks through more atom-economical strategies. However, despite these recent improvements and including the previous discoveries not mentioned here, critical gaps still remain. Most notably, the need for catalytic asymmetric methodologies toward chiral allenes that obviate the demand for synthetically challenging starting materials (ironically, many still utilize allenes as substrates) continues to be a formidable challenge. Likewise, the design of catalysts with broad applicability and ease of synthetic tractability will undoubtedly be a driving force for future innovations that will be applicable to both academic and industrial settings. Even more pressing is the ability to access chiral trisubstituted and tetrasubstituted chiral allenes with absolute control of not only stereochemistry but also substitution patterns around the allene core. In this regard, we view the development of even racemic catalytic methodologies toward highly substituted allenes as an unmet synthetic need that deserves immediate attention from the synthetic community. More broadly, we believe that catalytic approaches via unique mechanistic pathways toward allenes that complement current methodologies may ultimately prove most valuable in expanding the repertoire of allenes in the synthetic chemist's toolbox.

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Notes

The authors declare no competing financial interest.

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