A Neutral $PC_{NHC}P$ Co(I)-Me Pincer Complex as a Universal Catalyst for N-Allylic Isomerization.

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Supporting Information Placeholder

ABSTRACT: Earth-abundant metal catalyzed double bond transposition offers a sustainable and atom economical route towards the synthesis of internal alkenes. With emphasis specifically on internal olefins and ethers, the isomerization of allylic amines has been particularly underrepresented in the literature. Herein, we report an efficient methodology for the selective isomerization of *N*-allylic organic compounds including, amines, amides, and imines. The reaction is catalyzed by a neutral $PC_{NHC}P$ Cobalt(I) pincer complex and proceeds via a π-allyl mechanism that includes an unusual 1,2-methyl migration. The isomerization occurs readily at 80 °C and it is compatible with a wide variety of functional groups. The *in-situ* formed enamines, could additionally be used for a one-pot inverse-electron-demand Diels-Alder reaction to furnish a series of diversely substituted hetero-biaryls, which is further discussed in this report.

INTRODUCTION

Alkenes are ubiquitous in wide variety of natural and industrial products. The selective transposition of terminal carbon-carbon bond to internal ones has been investigated for decades mainly with precious metal catalysts (e.g., Pd, Ru and Ir).[1] Recently, significant efforts have been made to replace those precious metals with their earth-abundant congeners such as iron, cobalt, and nickel.[2] Using these metals has resulted in hall-mark examples of earth-abundant metal catalyzed double bond migration (**Figure 1**), where the emphasis has mainly been on olefins and allyl ethers.[1a, 1d, 2a, 3] By contrast, double bond migration from an *N*-allyl motif has been underrepresented in the literature despite its presence in a variety of natural products, agrochemicals, and industrially relevant compounds.[3a, 4]

The isomerization of *N*-allylic framework enables a selective and atom-economical pathway to highly polarized *N*-(1-propenyl) or generally *N*-vinyl intermediates,[3a] whose enamines, enamides and aza-dienes are commonly used in cycloadditions,[5] cyclopropanations,[6] heterocycle synthesis,[7] halofunctionalizations,[8] and transition metal catalyzed C–C bond forming reactions.[9] In addition, the transition-metal catalyzed tandem isomerization of *N*-allylic double bonds followed by functionalization of the *in-situ* formed *N*-vinyl intermediate offers access to highly functionalized molecules that would be otherwise difficult to synthesize via other methods.[10] Furthermore, the added benefit of *N*-allyl isomerization is that in these reactions the regio- and stereoselectivity is often well-defined.[3a, 11]

Because of their synthetic utility, Otsuka and co-workers reported in the 1980's the first Co(I)-hydride catalyzed isomerization of two allylamines to their

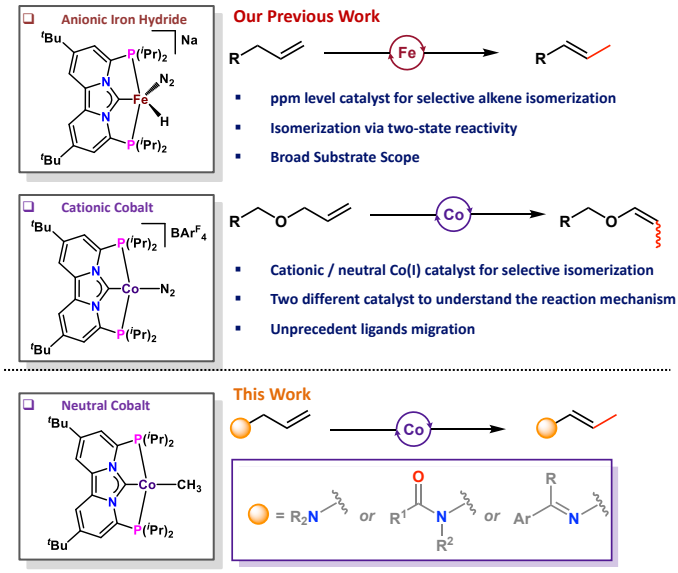


Figure 1. State-of-the-art Iron(0) and Cobalt(I) catalyst for alkene isomerization.

corresponding trans-enamines.[12] Stille on the other hand, demonstrated the ruthenium, rhodium, and iron catalyzed isomerization of allylamides to enamides, although different reaction conditions were necessary for each metal.[13] Later, the scope and stereoselectivity was greatly improved by Krompiec and co-workers who used noble metal containing catalysts.[3a, 14] Following these early examples, several recent studies reported the stereoselective isomerization of allyl amines and allyl amides.[1a, 4a, 4b, 15] Most notably, Trost and co-workers reported the isomerization of highly substituted *N*-allylamides to *Z*-enamides by utilizing a cationic ruthenium catalyst,[16] while Schoenebeck and co-workers used an air stable Pd(I) dimer for the *E*-selective synthesis of enamides.[17] Besides these hallmark examples, there are only a few studies who report the

transition-metal catalyzed isomerization of allyl imines to azadienes,[18] which is an interesting building block for the cycloaddition reactions. Overall, most of these reactions are catalyzed by precious metals, leaving ample opportunity to develop earth-abundant alternatives. Furthermore, no universal strategy has been developed that allows the isomerization of general *N*-allylic substrates such as allylamines, allylamides and allylimines, with a single catalyst, again leaving ample chemical space for such protocols to be developed.

Recently, our group reported efficient alkene isomerization catalyzed by well-defined iron(0) and cobalt(I) $PC_{NHC}P$ pincer complexes that proceeded either by an alkyl- (Fe) or allyl-type (Co) mechanism (**Figure 1**).[19] Building upon the success of these isomerization catalysts, herein, we report that the cobalt $PC_{NHC}P$ pincer complex [$(PC_{NHC}P)CoCH_3$] (**Co-Me**) is an excellent universal catalyst for the selective isomerization of allylamines, allylamides, allyl-aldimines, and allyl-ketimines (**Figure 1**). In addition, the resulting enamines were used in a one-pot sequential procedure for the inverse-electron-demand Diels-Alder reaction that enables facile synthesis of diversely substituted hetero-biaryls, which is further discussed in this report.

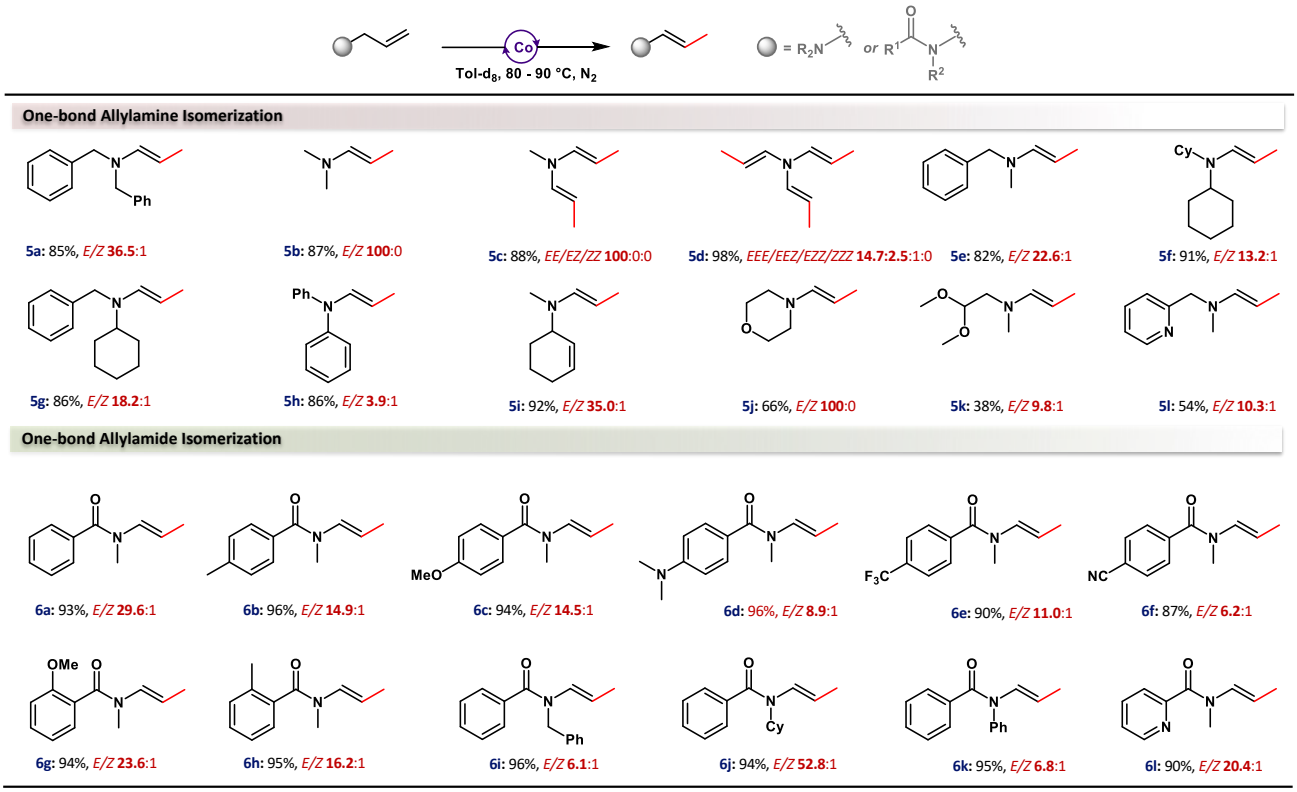
RESULTS AND DISCUSSION

Given our previous experiences in alkene isomerization, and the availability of a well-defined cobalt(I) $PC_{NHC}P$ pincer complexes, we sought to establish if [$(PC_{NHC}P)CoMe$)] (**Co-Me**) could efficiently isomerize *N*-allyllic substrates. To the best of our knowledge, there has been only one report on cobalt catalyzed isomerization of allylamines,[12] while no universal protocol is available to isomerize all three sets of *N*-allylic substates. We started our investigation into *N*-allylic isomerization with **Co-Me** as catalyst (5 mol%), *N*,*N*-dibenzylallylamine as a model substrate, and toluene-d_8 as solvent at 80 ˚C. Gratifyingly, the allylamine completely isomerized to the corresponding enamine with exceptional stereo-selectivity (*E*/*Z*: 37:1). A short optimization protocol revealed that the resulting enamine could also be obtained in excellent yields with 2 mol% of catalyst. (**Table S1**). Using the optimized conditions, we explored a diverse set of electronically or sterically differentiated allylamines (**Table 1**). As evident from **Table 1**, allylamines substituted with alkyl, aryl, cycloalkyl, heterocycles, diallyl, and triallyls substituents are all well tolerated, and their isomerization proceeded smoothly with excellent stereoselectivity. Sterically encumbered substrates such as *N*,*N*-dicyclohexyl or *N*,*N*-diphenyl allylamines, or a combination therefor, all provided the corresponding enamines (**5f**–**5h**) in excellent yield, although slightly higher temperatures were required for isomerization of *N,N*-diphenyl allylamine. Interestingly, heteroatom-substituted allylamines were also well tolerated (**5j–5l**) and the isomerization proceeded with complete conversion although the isolation of resulting enamine resulted in somewhat moderate yields.

Besides enamines, we were also interested if **Co-Me** could be used to isomerize *N*-allylamides, since the resulting enamides are extensively utilized in various organic transformations.[5c, 5d, 20] Although several methods are available for their synthesis,[21] transition metal catalyzed isomerization is one of the most convenient and atom-economical routes.[4a, 4b, 16-17] Consequently, we set out to test the isomerization of *N*-allylamides with our previous established reaction protocol (**Table 1**). Gratifyingly, the isomerization of *N*-allyl-*N*-methylbenzamide proceeded readily at 80 °C and produced the corresponding enamide with excellent stereoselectivity (**Table 1**; **6a**). Changing the nature of the benzamide to include electron-donating (e.g., –Me, –OMe, or $-NMe_2$) or electron withdrawing substituents (e.g., –CN or $-CF_3$), did not affect the yield nor stereoselectivity of the reaction (**Table 1**; **6b**–**6f**). Likewise, changing the substituent pattern at the arene-ring did not affect yield nor stereoselectivity (**Table 1**; **6g** and **6h**). To investigate how sterics parameters influence the isomerization reaction, we modified the *N*-methyl substituent to either benzyl, phenyl, or cyclohexyl. In all cases the corresponding enamide (**6i**–**6k**) were obtained in good yields (> 94%) with moderate to excellent *E*-stereoselectivity (*E*/*Z* >= 6:1). Even *N*-allyl-*N*-methyl-picolinamide could be isomerized with excellent *E*-selectivity (**Table 1**; **6l** *E*/*Z*: 20.4:1). These results demonstrate that our recently reported **Co-Me** complex is a excellent catalyst for the stereoselective isomerization of *N*-allylamines and *N*-allylamides.

Driven by the successful isomerization of these substrates, we sought to provide easy access to 1,3-azadienes via isomerization of *N*-allylimines. While useful substrates in organic syntheses, accessing the 1,3-azadiene motif is difficult and, frequently relies on base-mediated isomerization of allylimines that proceeds with poor yields and selectivity.[22] Recently a different route was reported by Trost and co-workers who accessed the azadiene via a palladium catalyzed oxidative allylic alkylation.[23] To the best of our knowledge there has been no report on first-row transition metal catalyzed one-bond isomerization of *N*-allylimines.

Table 1. Isomerization of *N*-allylamines and *N*-allylamides catalyzed a neutral Co(I)-Me catalyst.[a]



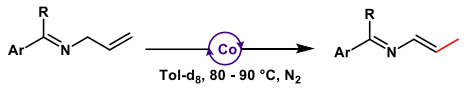
[a]Reactions were performed with 2-5 mol% catalyst, 0.15 mmol substrate, in 400 µL toluene-d_8 for 6-24 hours at 80–90 ˚C. Yields and stereoselectivity (*E* vs. *Z*) were determined by ^{1}H and ^{13}C NMR spectroscopy.

To test the isomerization of *N*-allylimines, we selected phenyl aldimine as benchmark substrate with **Co-Me** as catalyst. Using the optimized reaction conditions (*vide supra*) the corresponding 2-aza-1,3-dienes (**7a**) was obtained in 94% yield. Compared to the isomerization of *N*-allylamines and amides, the *E*-stereoselectivity is only moderate (*E*:*Z* = 2.2:1), which is expected for such substrates. Further exploring the substrate scope revealed that electronically differentiated phenyl aldimines are isomerized efficiently, where both electron donating (e.g., -Me, –OMe and –NMe_2) or electron withdrawing (e.g., –CN or –CF_3) substituents are well tolerated (**Table 2; 7b–7f**). Furthermore, *ortho* substitution on the phenyl ring (**7g**) did not impede the transformation. Similarly, the tri-substituted aryl (**7j**) and 1-napthyl (**7k**) allylimines were also tolerated, albeit longer reaction times were necessary to obtain complete conversion of the substrate. To our delight, non-aromatic (**7l**) and hetero-aromatic (**7h**, **7i**) allylimines were efficiently isomerized to the corresponding 2-aza-1,3-dienes in good to moderate yield. Finally, we were also able to extend this methodology to include *N*-allylketimines. Akin to their imine congeners, similar yields and stereoselectivities were obtained (**Table 2; 8a–8l**), although slightly higher temperatures (90 °C) were required to complete the reaction.

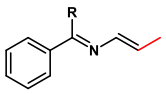
Considering the importance of 2-aza-1,3-dienes as substrates in organic chemistry, the isomerized products can be readily converted into other six-membered heterocycles,[23] via an inverse-electron-demand Diels-Alder cycloaddition (**Scheme 1A**). The one-step formation of pyridine containing motifs would be a valuable asset in the synthesis of natural products and pharmaceuticals. We performed this cycloaddition with electron deficient 2-aza-1,3-diene **7a** and enamine **11** in the presence of $MgBr_2{\cdot}Et_2O$ as promotor. Subsequent oxidation with Pd/C resulted in the formation of various hetero-biaryls as single regioisomers in low to moderate yield (**9a-9c**). Note that in the study by Trost and co-workers, similar yields were obtained for a multi-step synthesis. Realizing that enamine coupling partner could also be accessed via our isomerization protocol, we envisioned developing a one-pot procedure where both the 2-aza-1,3-diene and the enamine starting materials are obtained via our cobalt catalyzed isomerization protocol. To test the one-pot cycloaddition, *N*-allyl morpholine and phenyl aldimine were mixed in a J-Young tube and the reaction was heated at 80 ˚C with 5 mol% **Co-Me** catalyst. Unfortunately, only the phenyl aldimine was completely converted to the 2-aza-1,3-diene, with less than 5% conversion of the *N*-allylamine. Even increasing the reaction time and catalyst loading did not improve the conversion of *N*-allylamine to the

corresponding enamine. Most likely, strong coordination of 2-aza-1,3-diene to the cobalt metal centers prevents further isomerization of the *N*-allylamine. Indeed, when first *N*-allyl morpholine was added to a mixture of **Co-Me** in toluene-d_8, complete isomerization was observed as reported in Table 1. Subsequent addition of the *N*-allylaldimine resulted in quantitative formation of 2-aza-1,3-diene, as judged by ^{1}H NMR spectroscopy. With both substrates now available through cobalt catalyzed isomerization, a sequential one-pot procedure was developed for the synthesis of diversely substituted 2-phenyl pyridines (**Scheme 1B**). To illustrate, in a one-pot procedure, *N*-allyl morpholine was isomerized with 5 mol% Co-Me catalyst at 80 ˚C. Subsequent addition of the aryl aldimine to the same reaction mixture resulted in the formation of the 2-aza-1,3-diene product. To facilitate the Diels-Alder reaction, $MgBr_2{\cdot}Et_2O$ was added followed by Pd/C to furnish the desired pyridine-biaryl as a single regio-isomer as product (**Figure S123-124**). This methodology is wide applicable and can be used to access both electron rich and electron poor 2-phenylpyridines (**10a**–**10c**) in moderate to excellent yields (**Scheme 1B**).

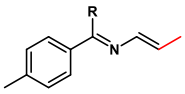
Table 2. Isomerization of *N*-allylaldimines and *N*-allylketimines catalyzed by a neutral Co(I)-Me catalyst.[a]



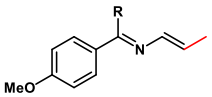
One-bond Allylaldimine and Allylketimine Isomerization



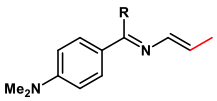
7a: R = H, 94%, *E*/*Z* **2.2**:1
8a: R = Me, 92%, *E*/*Z* **2.0**:1



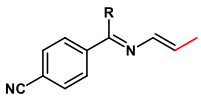
7b: R = H, 91%, *E*/*Z* **2.1**:1
8b: R = Me, 93%, *E*/*Z* **1.8**:1



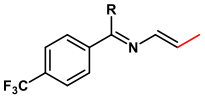
7c: R = H, 93%, *E*/*Z* **2.5**:1
8c: R = Me, 95%, *E*/*Z* **2.8**:1



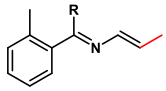
7d: R = H, 94%, *E*/*Z* **2.3**:1
8d: R = Me, 91%, *E*/*Z* **3.8**:1



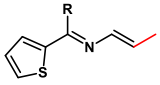
7e: R = H, 87%, *E*/*Z* **2.1**:1
8e: R = Me, 93%, *E*/*Z* **1.5**:1



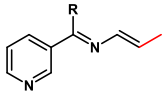
7f: R = H, 90%, *E*/*Z* **2.5**:1
8f: R = Me, 93%, *E*/*Z* **2.4**:1



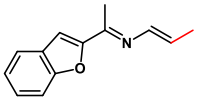
7g: R = H, 92%, *E*/*Z* **2.2**:1
8g: R = Me, 97%, *EE*/*EZ*/*ZE*/*ZZ* **9.2**:2.9:2.1:1



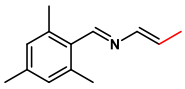
7h: R = H, 91%, *E*/*Z* **2.1**:1
8h: R = Me, 91%, *E*/*Z* **2.1**:1



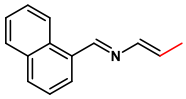
7i: R = H, 76%, *E*/*Z* **2.1**:1
8i: R = Me, 89%, *E*/*Z* **2.4**:1



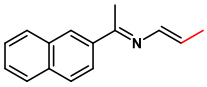
8j: 70%, *E*/*Z* **1.7**:1



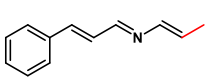
7j: 95%, *E*/*Z* **1.9**:1



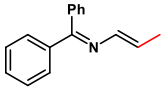
7k: 82% ,*EE*/*EZ*/*ZE*/*ZZ* **13.9**:6.9:2.6:1



8k: 89%, *E*/*Z* **2.5**:1



7l: 36%, *E*/*Z* **4.8**:1



8l: 90%, *E*/*Z* **2.1**:1

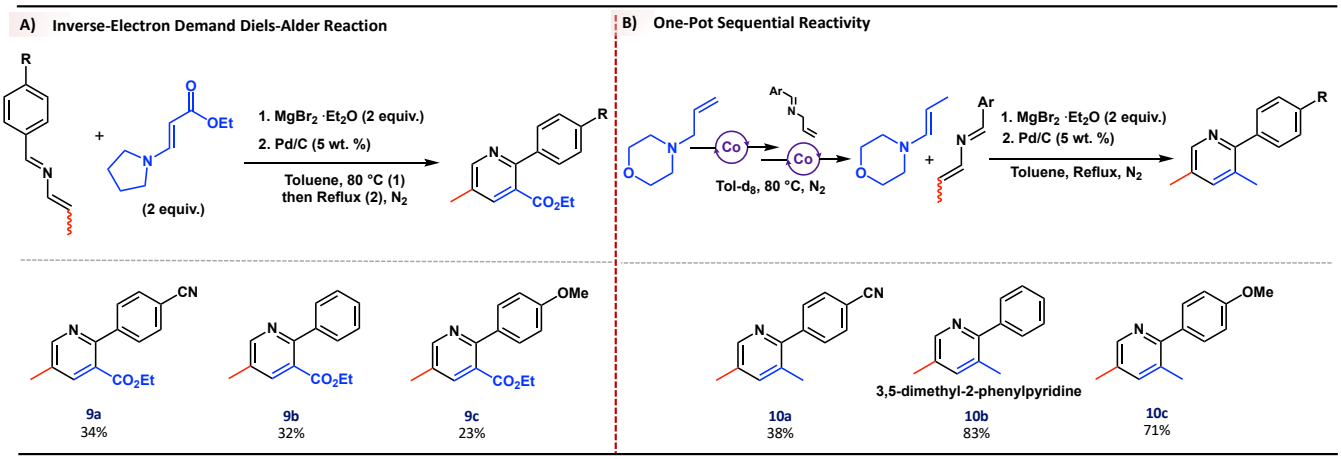
[a]Reactions were performed with 5 mol% catalyst, 0.15 mmol substrate, in 400 µL toluene-d_8 for 6-24 hours at 80–90 ˚C. Yields and stereoselectivity (*E* vs. *Z*) were determined by ^{1}H and ^{13}C NMR spectroscopy

Mechanistically, we have previously shown that the isomerization reaction occurs via a π-allyl mechanism that, included an unprecedented reversible 1,2-migration of the methyl substituent on cobalt to the NHC carbon. We envisioned that such a mechanism is also operable for the isomerization of *N*-allyllic substrates to generate the respective *N*-vinyl products. However, in the case of *N*-allylimines, two intermediates are possible during the isomerization process: (i) an all-carbon-π-allyl Co(III) complex and (ii) a 2-aza-π-allyl Co(III) complex, that are most likely in equilibrium. Our experiments indicate that for the *N*-allylimines, 2-aza-1,3-dienes are the sole product of the reactions with no trace of the 1-azadienes, which suggest that the reaction follows through all-carbon-π-allyl Co(III) intermediate.

CONCLUSION

In conclusion, we have established the versatility of neutral **Co(I)-Me** complex as an efficient catalyst for the isomerization of *N*-allyl substrates. The isomerization of *N*-allylamines, *N*-allylamides, and *N*-allylimines exhibited excellent *E*-stereoselectivity, occurred under moderate conditions and is compatible with a wide variety of functional groups that include electron-donating, electron-withdrawing and heteroaromatics substituents. Furthermore, the **Co(I)-Me** catalyzed isomerization protocol could be extended to a sequential one-pot inverse-electron-demand Diels-Alder reaction to give access to diversely substituted 2-phenylpyridines. To the best of our knowledge, the herein reported methodology represents the first example of a single catalyst that is able to tackle the isomerization of any kind of *N*-

allyllic substrate under mild reaction conditions. Current efforts are directed to develop Z-selective protocols and to enable the isomerization of di-, and tri-substituted alkenes, which are currently problematic.



Scheme 1. Inverse electron-demand [4+2] Diels-Alder cycloaddition for hetero-aryl synthesis. One-pot sequential reactivity for hetero-aryl synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at the ACS website.

Synthetic procedures, characterization data, and catalysis (PDF)

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