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Synthesis of Azepines by a Gold-Catalyzed Intermolecular [4 + 3]-Annulation

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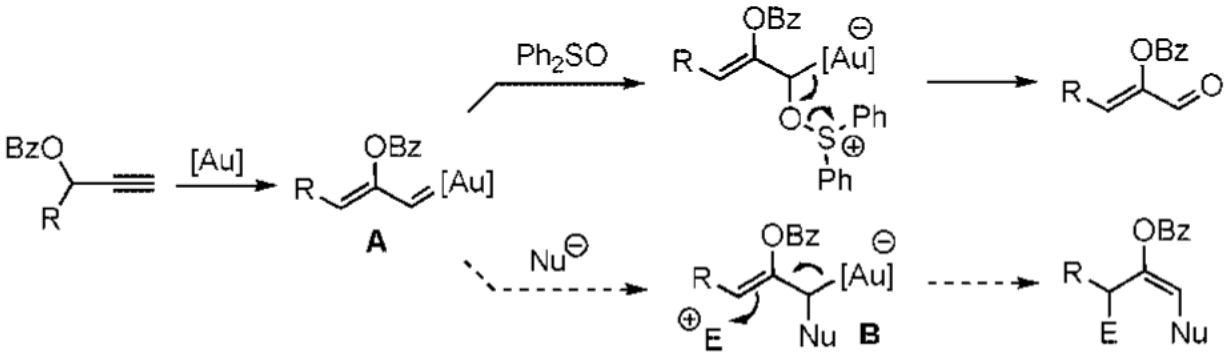
Gold catalysis has recently generated a variety of valuable methods for the synthesis of complex structures from simple starting materials.[1] While the majority of efforts have focused on intramolecular rearrangement and addition reactions, a number transformations taking advantage of intermolecular reaction of the a gold-stabilized cationic intermediate generated from the 1,2-rearrangement of propargyl esters have been described.[2] In these reactions, the cationic intermediate shows reactivity analogous to that reported for electrophilic metal-stabilized vinylcarbenoids.[3-5] For example, we have shown that sulfoxides react with intermediate **A** to form carbonyl compounds (eq 1).[5] On the basis of this reactivity, we postulated that allylgold intermediate **B**, generated by reaction of **A** with a nucleophile, could be induced to react with electrophiles. Herein, we report the realization of this goal leading to a convenient method for the construction of azepines.



(1)

In analogy to related reactions of rhodium-stabilized vinylcarbenoids,[6] we reasoned that generation of allylgold intermediate **B** and a proximate electrophile could be accomplished by reaction of **A** with a nucleophilic diene, such as an α,*β*-unsaturated imine. On the basis of this hypothesis, we were pleased to find that subjecting propargyl ester **1** and *N*-phenyl imine **2** to our typical conditions for cationic triphenylphosphinegold(I)-catalyzed reactions afforded a trace amount of azepine **3** (Table 1, entry 1). While changing the ligand from triphenylphosphine to an N-heterocyclic carbene only slightly improved the yield (entry 2), the use of 5 mol % of AuCl allowed for the formation of azepine **3** in 44% yield (Table 1, entry 3). On the basis of reports that suggest AuCl may form Au(III) species in situ,[7] we subsequently examined Au(III) sources and were pleased to find that picolinic acid derived catalyst **4** catalyzed formation of the desired product with increased efficiency (65% yield, entry 5).[8]

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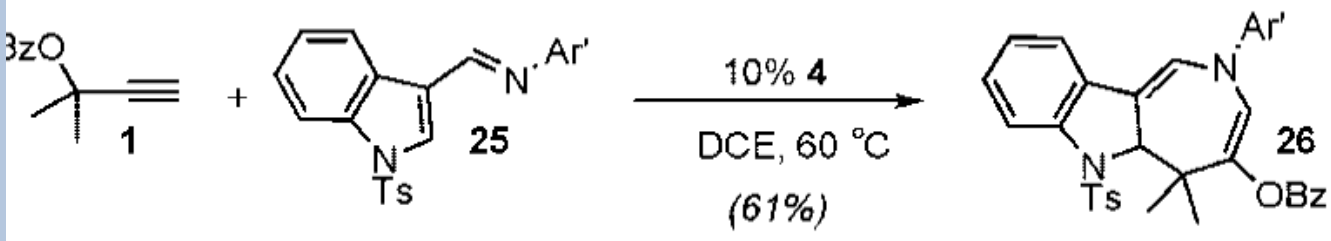
With conditions in hand, we examined the scope of the gold-catalyzed [4 + 3]-cycloaddition (Table 2). In general, the highest yields were obtained with substrates containing electron-rich *N*-aryl groups on the imine nitrogen (entries 1-5). On the other hand, the reaction proved highly tolerant of variation at the other positions of the unsaturated imine component. For example, having the olefin conjugated with electron-rich and electron-deficient aryl groups had little impact on the yield of the cycloaddition (entries 6 and 7). The olefin substituents can also be aliphatic. For example, imine **9** underwent chemoselective [4 + 3]-cycloaddition to afford **10** in 60% yield without cyclopropanation of the isolated alkene (entry 9). Additionally, gold-catalyzed cycloaddition of vinyl bromide **11** produced a 63% yield of bromoazepine **12**, a potential cross-coupling partner (entry 10).

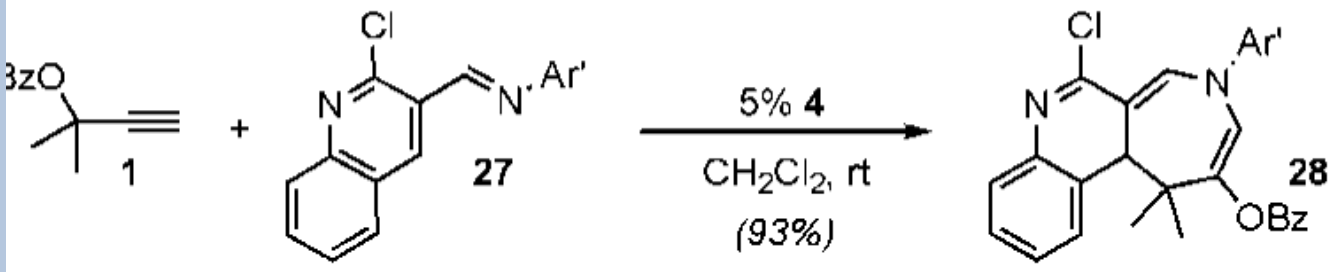
We next turned to examine the scope of the propargyl ester component of the cycloaddition (Table 3). With secondary benzylic propargyl esters **13** and **15**, the reactions provided azepine products **14** and **16** in good yields and as single diastereomers (entries 1 and 2).[9] Tertiary propargyl esters also participated in the cycloaddition addition, smoothly affording all-carbon quaternary centers in azepines **18** and **20**, albeit with diminished diastereocontrol (entries 3 and 4). Similarly, *tert*-butylcyclohexanone derived ester **21** underwent the gold-catalyzed cycloaddition to generate **22** with 2.5:1 dr with respect to the axial stereocenter (entry 5).

A proposed mechanism that accounts for this diastereoselectivity is detailed in Scheme 1. Gold-promoted isomerization of the propargyl ester leads to gold-carbenoid intermediate **A**.[10,11] Subsequent nucleophilic addition of the imine nitrogen generates allylgold intermediate **23** that undergoes intramolecular nucleophilic addition onto the pendant iminium electrophile via transition state **24**.

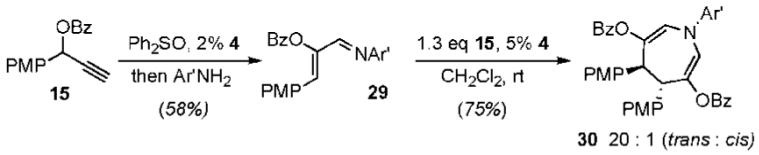
Additional studies revealed that electron-donating substituents on the *N*-aryl and *β*-aryl groups enhance the rate of the gold-catalyzed cycloaddition, supporting a stepwise mechanism in which formation of iminium **23** is rate-determining.[12] On the basis of this observation, we envisioned that heteroaryl imines might also serve as heterodienes in the gold-catalyzed [4 + 3]-cycloaddition. We were pleased to find that indole azepine **26** was formed from the gold-catalyzed cycloaddition of **1** with imine **25**, albeit at slightly elevated temperatures and increased catalyst loading (eq 2). On the other hand, quinoline imine **27** underwent gold-catalyzed coupling with propargyl ester **1** to furnish tricyclic azepine **28** in 93% yield at room temperature (eq 3).



(2)



(3)



(4)

In conclusion, we have developed a Au(III)-catalyzed synthesis of azepines via the annulation of simple, readily available starting materials. This is exemplified by the fact that both components employed in the cycloaddition reaction to form azepine **30** can be generated from gold-catalyzed rearrangements of propargyl ester **15** (eq 4). In addition to representing a rare example of a Au-catalyzed intermolecular annulation reaction,[13] the [4 + 3]-cycloaddition highlights the generation and subsequent electrophilic trapping of an allyl-gold intermediate from gold-stablized vinylcarbenoid **A**. The development of reactions that take advantage of this mechanistic paradigm is ongoing in our laboratories and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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References

(1). For recent reviews of gold-catalyzed reactions, see:(a)Jiménez-Nunez E, Echavarren AM. Chem. Commun 2007:333.(b)Gorin DJ, Toste FD. Nature 2007;446:395. [PubMed: 17377576](c)Furstner A, Davies PW. Angew. Chem., Int. Ed 2007;46:3410.(d)Hashmi ASK. Chem. Rev 2007;107:3180. [PubMed: 17580975](e)Shen HC. Tetrahedron 2008;64:3885.

(2). (a) Marion N, Nolan SP. Angew. Chem., Int. Ed 2007;46:2750. (b) Correa A, Marion N, Fensterbank L, Malacria M, Nolan SP, Cavallo L. Angew. Chem., Int. Ed 2008;47:718.

(3). (a) Miki K, Ohe K, Uemura S. J. Org. Chem 2003;68:8505. [PubMed: 14575478] (b) Johansson MJ, Gorin DJ, Staben ST, Toste FD. J. Am. Chem. Soc 2005;127:18002. [PubMed: 16366541] (c) Gorin DJ, Dube P, Toste FD. J. Am. Chem. Soc 2006;128:14480. [PubMed: 17090030] (d) Gorin DJ, Watson IDG, Toste FD. J. Am. Chem. Soc 2008;130:3736. [PubMed: 18321110]

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(6). (a)Doyle MP, Hu W, Timmons DJ. Org. Lett 2001;3:3741. [PubMed: 11700127](b)Doyle MP, Yan M, Hu W, Gronenberg LS. J. Am. Chem. Soc 2003;125:4692. [PubMed: 12696871](c)Davies HML, Hu B, Saikali E, Bruzinski PR. J. Org. Chem 1994;59:4535.For a related reaction of Fischer carbenes, see:(d)Barluenga J, Tomás M, Ballesteros A, Santamaria J, Carbajo RJ, López-Ortiz F, Garcia-Granda S, Pertierra P. Chem.—Eur. J 1996;2:88.(e)Barluenga J, Tomás M, Rubio E, Lopez-Pelegrin JA, Garcia-Granda S, Priede MP. J. Am. Chem. Soc 1999;121:3065.(f)Barluenga J, Tomás M, Rubio E, Lopez-Pelegrin JA, Garcia-Granda S, Priede MP. J. Am. Chem. Soc 1999;121:3065.

(7). Lemiere G, Gandon V, Agenet N, Goddard JP, de Kozak A, Aubert C, Fensterbank L, Malacria M. Angew. Chem., Int. Ed 2006;45:7596.

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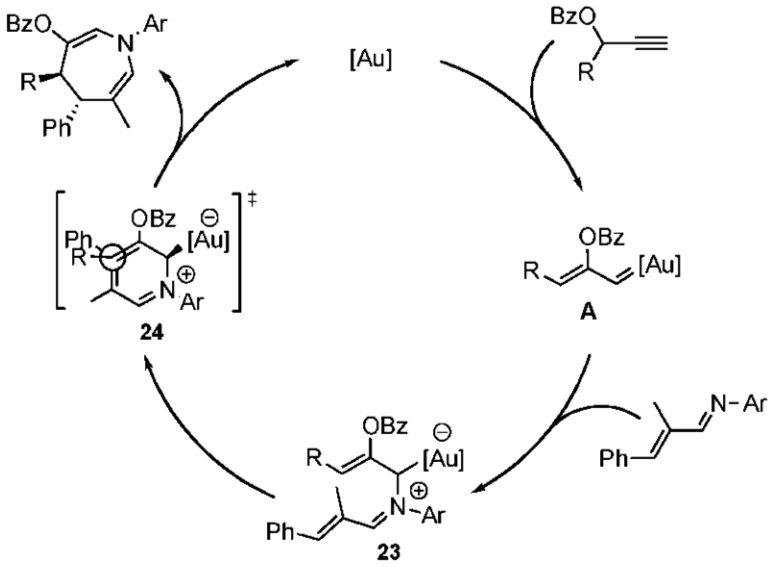
(9). The *trans*-diaryl stereochemistry, which is opposite to that produced in related rhodium-catalyzed cycloadditions,6a was established by an X-ray crystal structure (see Supporting Information) of **13**.

(10). As in the intermolecular cyclopropanation of these intermediates,3b chirality was not transferred in the cycloaddition of enantioenriched propargyl ester **15** with imine **2b** (see Supporting Information).

(11). The observation that the *E*/*Z*-selectivities obtained by trapping with sulfoxides are not identical to the diastereoselectivity observed in the cycloaddition suggests that **A** is formed reversibly2b and reacts with nucleophile dependent selectively (see Supporting Information).

(12). See Supporting Information for details.

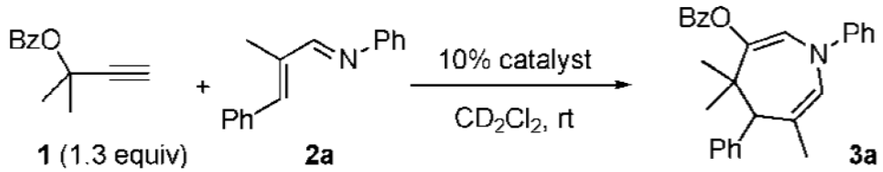
(13). For additional examples of intermolecular gold-catalyzed annulations, see:(a)Melhado AD, Luparia M, Toste FD. J. Am. Chem. Soc 2007;129:12638. [PubMed: 17900190](b)Hsu Y-C, Datta S, Ting C-M, Liu R-S. Org. Lett 2008;10:521. [PubMed: 18184002](c)Zhang G, Huang X, Li G, Zhang L. J. Am. Chem. Soc 2008;130:1814. [PubMed: 18205360](d)Barluenga J, Fernández-Rodríguez MA, García-García P, Aguilar E. J. Am. Chem. Soc 2008;130:2764. [PubMed: 18266378]



Scheme 1.
Mechanistic Hypothesis

Table 1

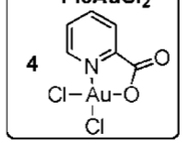
Optimization of the Au-Catalyzed [4 + 3]-Cycloaddition



1 (1.3 equiv) **2a** **3a**

entry	catalyst	time (h)	yield (%)[a]
1	$Ph_3PAuCl + AgsbF_6$	24	6
2	$IMesAuCl + AgSbF_6$	24	17
3	AuCl	4	44
4	$AuCl_3$	4	33
5	$PicAuCl_2$ (5%)	2	65

PicAuCl$_2$



[a]By ^{1}H NMR versus an internal standard.

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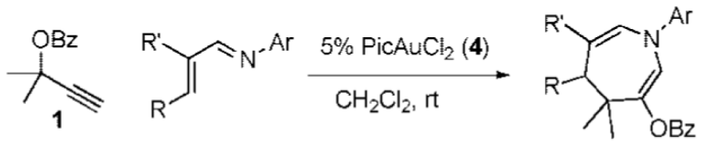
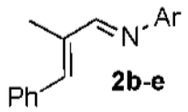
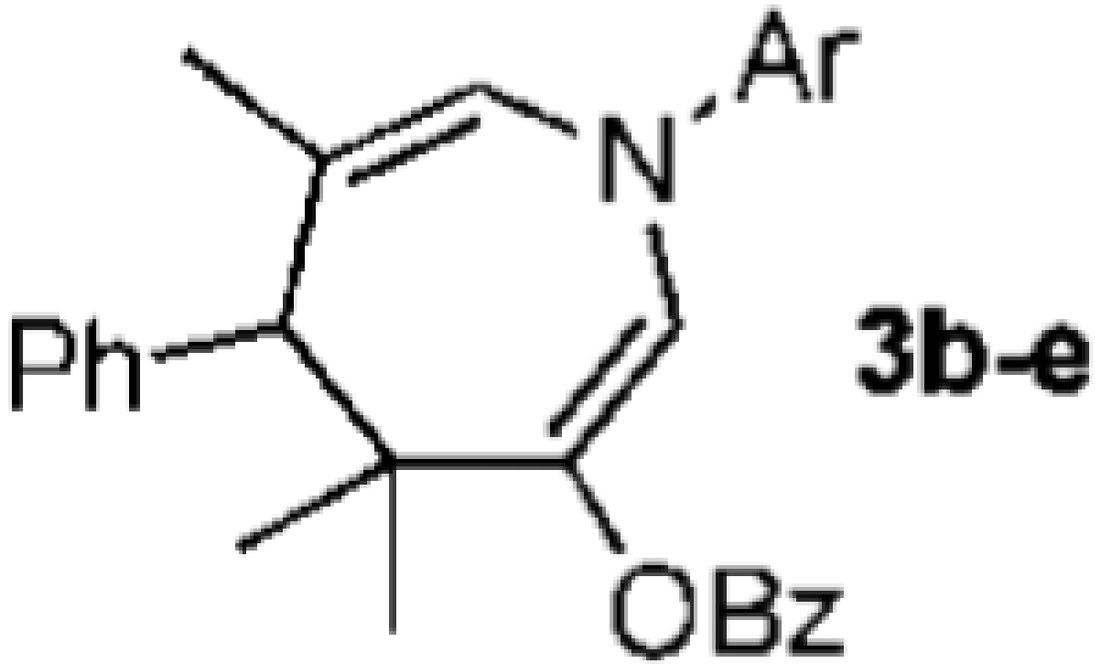
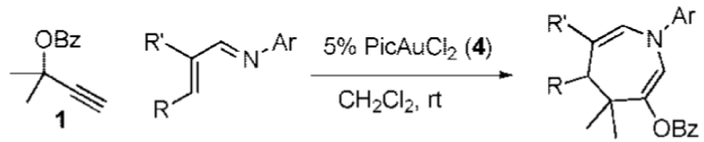
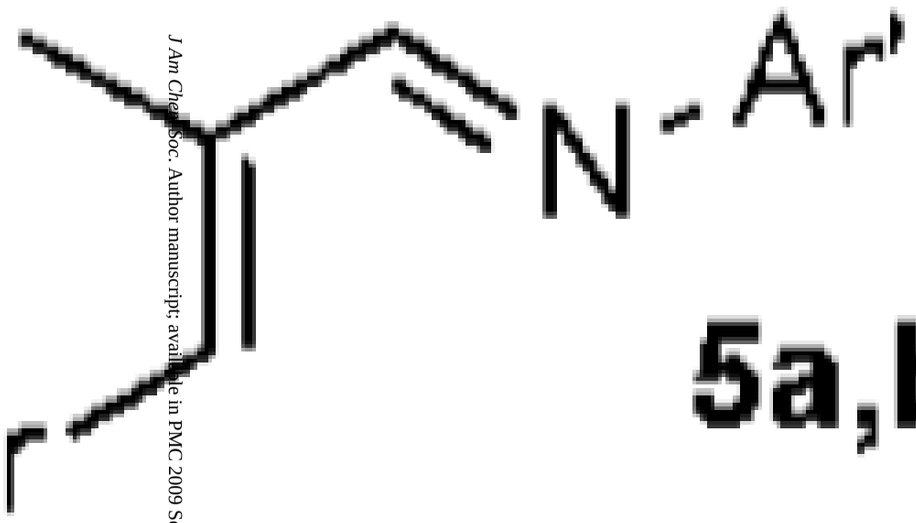
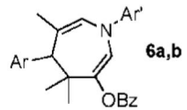
Table 2

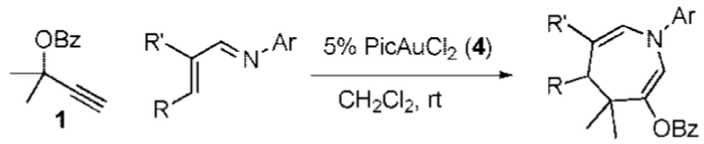
loaddition of α,β-Unsaturated Imines

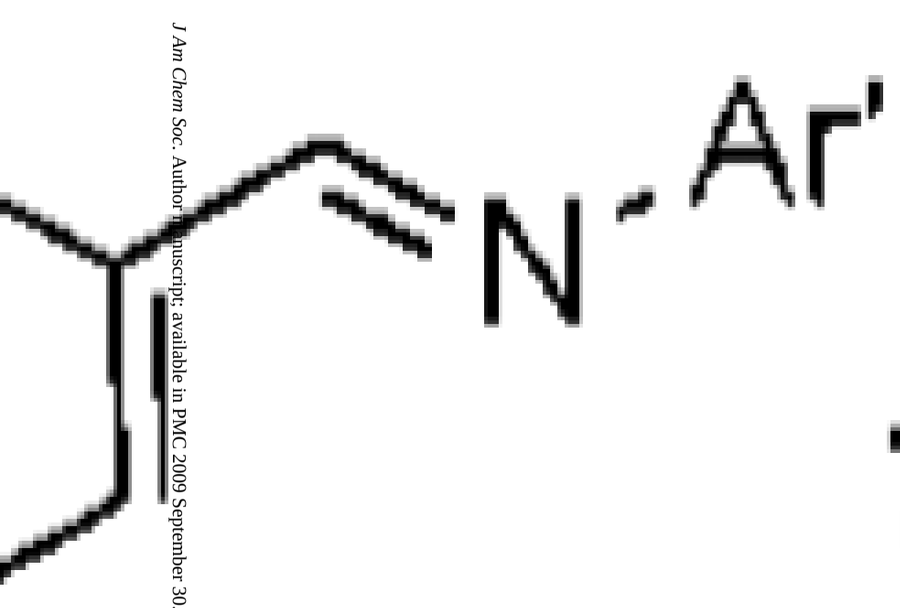
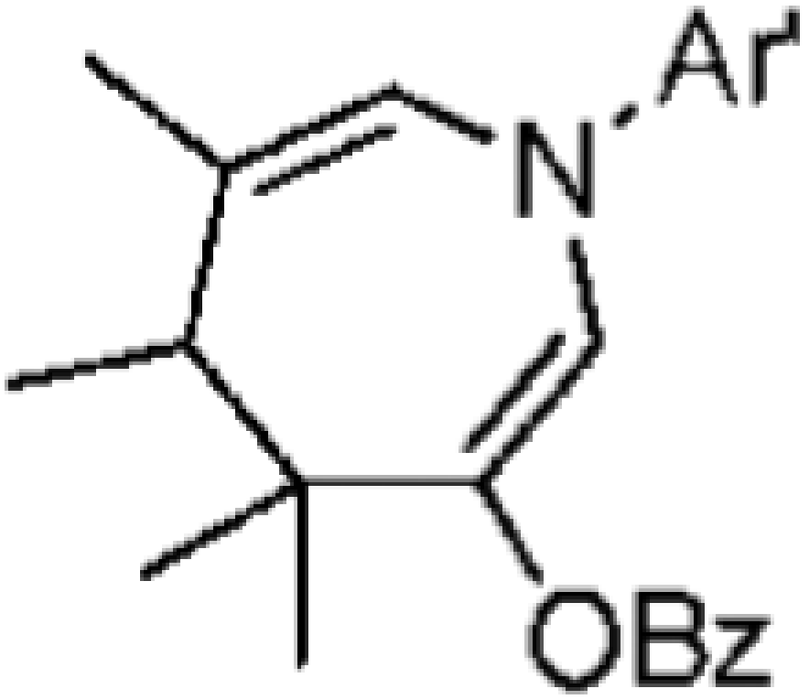


imine	azepine	Yield
 **2b-e**	 **3b-e**	**b** Ar = 4-HO-2,6-Me_2-C_6H_2 *87%* **c** Ar = 2,6-Me_2-C_6H_3 *80%* **d** Ar = 2,3-Me_2-C_6H_3 *88%* **e** Ar = 4-MeO-C_6H_4 *65%*
		f Ar = 4-F-C_6H_4 *55%*



imine	azepine	Yield
 **5a,b**	 **6a,b**	**a** Ar = 4-$NO_2C_6H_4$ *70%* **b** Ar = 4-$MeOC_6H_4$ *80%*



imine	azepine	Yield
 7	 8	*65%*

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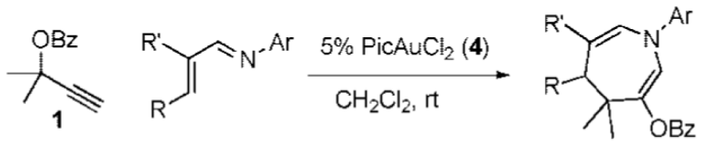
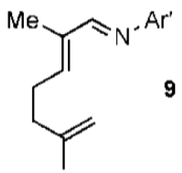
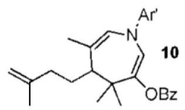
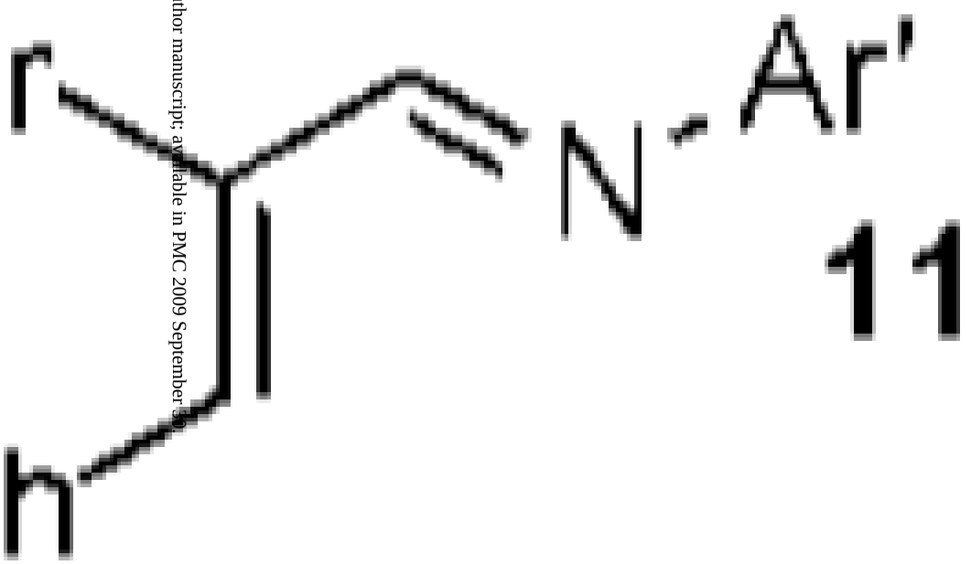
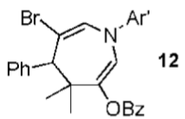
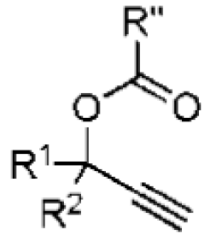


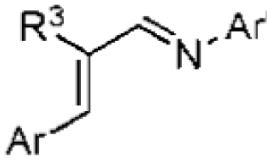
imine	azepine	Yield
 **9**	 **10**	*62%*
 **11**	 **12**	*63%*

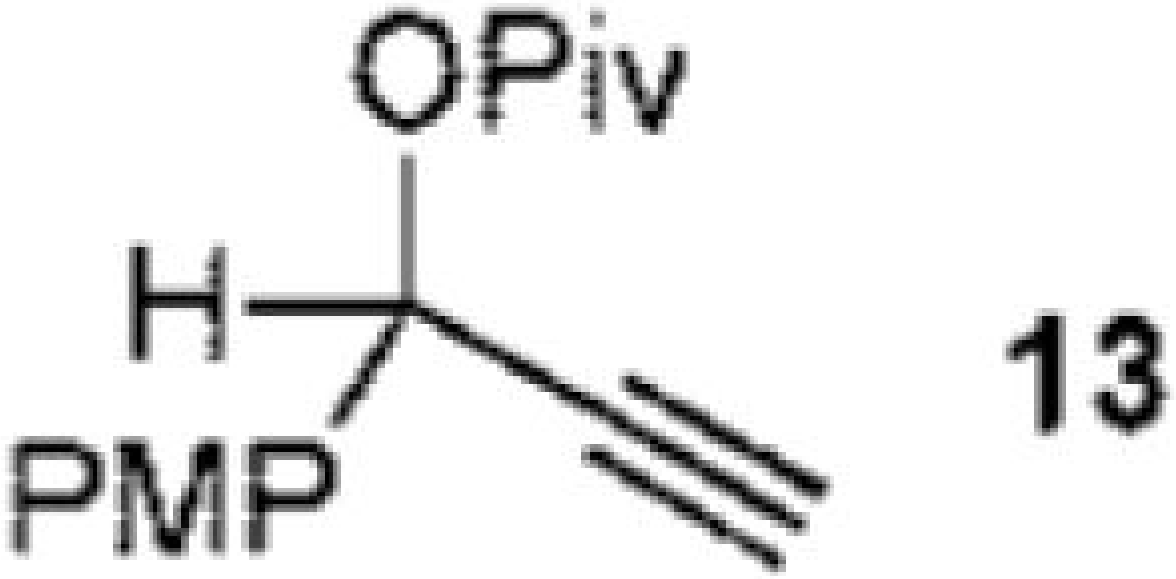
CH_2Cl_2, rt. Ar' = 4-HO-2,6-Me_2-C_6H_2.

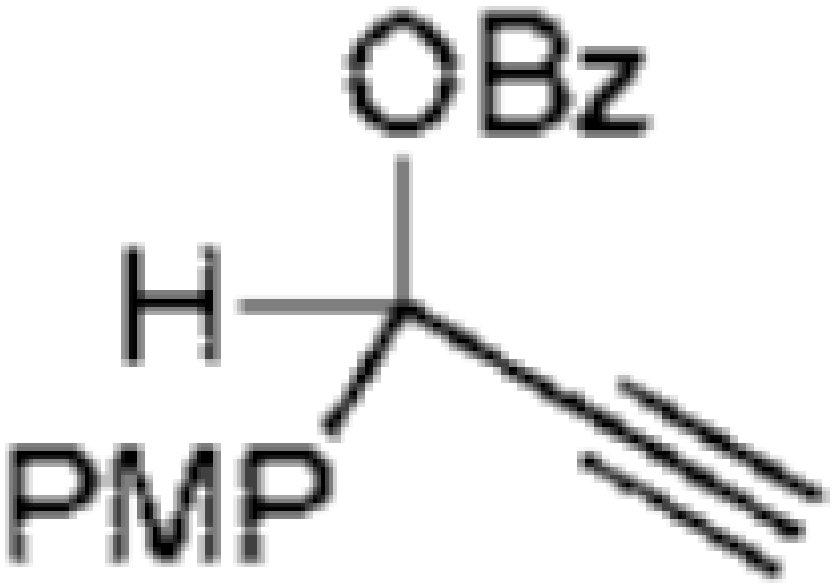
Table 3

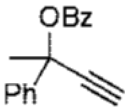
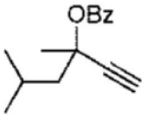
Diastereoselective Transformations of Propargyl Esters

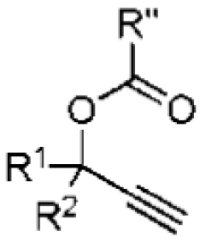


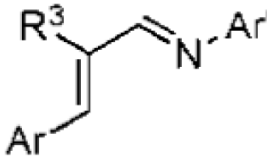


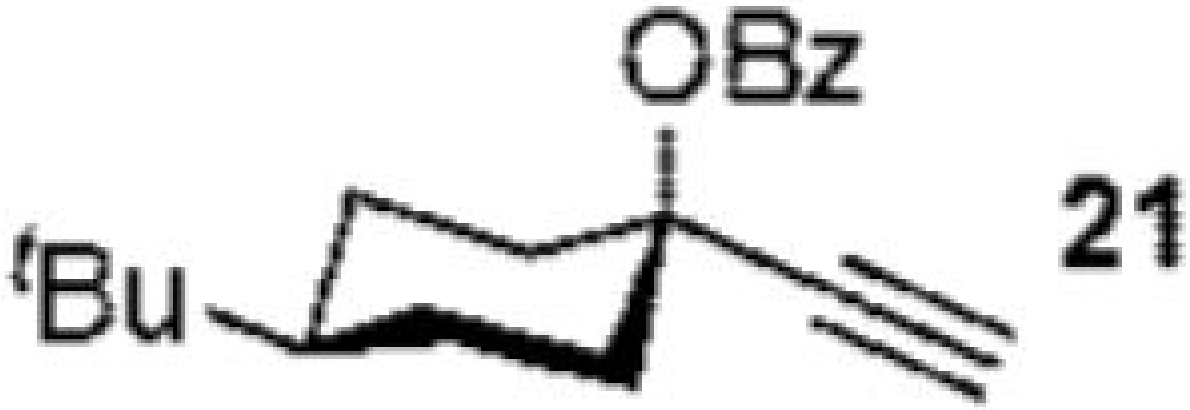
entry	propargyl ester	imine
1		**5a**

entry	propargyl ester		imine
2		15	11

entry	propargyl ester	imine
3	 **17**	**2b**
4	 **19**	**2b**





entry	propargyl ester	imine
5		2b

[a] Conditions: 1.3 equiv of propargyl ester, 5% **4**, CH_2Cl_2, rt.

[b] Conditions: 2 equiv of propargyl ester, 10% 4, dichloromethane, 60 °C. Ar' = 4-HO-2,6-Me_2-C_6H_2.