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Ring Expansion of Alkynyl Cyclopropanes to Highly Substituted Cyclobutenes via a *N*-Sulfonyl-1,2,3-Triazole Intermediate

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Abstract

Regioselective ring expansion of alkynyl cyclopropanes to highly substituted cyclobutenes was developed. The reaction involves a copper-catalyzed cycloaddition of an alkyne with an arylsulfonyl azide and a silver-catalyzed carbene formation followed by ring expansion of a cyclopropyl carbene intermediate.

Four-membered rings are frequently presented in bioactive natural products and employed as key intermediates for the preparation of complex targets.[1] Efficient synthesis of functionalized four-membered rings still stimulate the development of new selective methods that complements existing technologies.[2] We previously developed a method for the synthesis of highly substituted cyclobutenes from cyclopropyl metal carbenes derived from Rh(II), Ag(I), or Cu(I)-catalyzed decomposition of diazo compounds (Scheme 1).[3, 4] We took advantage of the well-documented stereoselective cyclopropanation methods[5] and transferred the substituents and stereochemistry of cyclopropanes to cyclobutenes.[6] This method was recently applied to the diastereo- and enantioselective synthesis of the proposed structures of natural products pipercyclobutanamide A and piperchabamide G.[7] However, cyclopropyl diazo compound **1** is not very stable and its preparation is often lengthy.

To search for a more convenient and stable precursor for cyclopropyl carbenes, we turned our attention to *N*-sulfonyl 1,2,3-triazoles,[8] a diazo compound equivalent developed by Fokin and Gevorgyan for annulation, cyclopropanation and C-H insertion reactions.[9, 10, 11] We found that cyclobutene carboxylaldehyde **6** could be prepared directly from alkynyl cyclopropane **4** through triazole intermediate **5** (Scheme 1), whose isolation was not necessary when two metal catalysts were employed.

Known aldehyde **8** was prepared by cyclopropanation of styrene with tosyl triazole **7**.[10, 11] Homologation of aldehyde **8** then afforded cyclopropyl acetylene **4a** (Scheme 2).[12] The acetylene in **4a** could be converted to tosyl triazole **9** following literature procedures.[13]

Triazole **9** was then treated with three catalysts that we previously used for the decomposition of cyclopropyl diazo compounds (Scheme 3).[3] Although $Rh_2(Oct)_4$ was a more reactive catalyst than AgOTf and $Cu(MeCN)_4PF_6$, the latter two provided much higher regioselectivity for the formation of cyclobutene **11** over isomer **12**. Through the formation of tosyl triazoles **7** and **9**, carbons 1 and 2 in intermediate **10** were converted to metal carbenes from alkynes conveniently.

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†Electronic Supplementary Information (ESI) available: [^{1}H NMR, ^{13}C NMR, HRMS, and IR data and copies of NMR specta for all starting materials and products.]. See DOI: 10.1039/b000000x/

We then examined the effect of arylsulfonyl azide on triazole formation and ring expansion (Scheme 4). It has been reported that the reactivity of *N*-sulfonyl 1,2,3-triazole increases and its stability decreases when the tosyl group was replaced by a triflate.[11] We prepared triazoles **14a-14c** from alkyne **4a** and azides **13a-13c**, respectively. We found that the ring expansion of triazole **14c** could be completed in 4h at room temperature in the presence of a Ag(I) catalyst, while low conversions were observed for triazoles **14a** and **14b** under the same condition. In the absence of any catalyst, no reaction was observed at room temperature after 24h. Triazole **14d** derived from alkyne **4a** and azide **13d** was not stable enough to be isolated. Triazole **14c** has the balanced reactivity and stability.

During the preparation of triazole **14c**, we also observed small amount of cyclobutene product **15c**, suggesting that CuTc was capable of catalyzing the decomposition of triazole. However, even after we extended the reaction time from 4h to 12h, the ratio of **15c**/**14c** was only about 1:2. Base on results in Scheme 3, AgOTf catalyst has higher reactivity than $Cu(MeCN)_4PF_6$ and higher selectivity than $Rh_2(Oct)_4$. We then decided to treat cyclopropyl acetylene **4a** with azide **13c** in the presence of both CuTc and AgOTf catalysts. We were pleased to find that these two catalysts did not interfere with each other and cyclobutene carboxyaldehyde **6a** was isolated in good yield and selectivity (entry 1, Table 1).

We then studied the scope of the ring expansion of different cyclopropyl acetylenes facilitated by the dual catalyst in the presence of azide **13c** (Table 1). We first examined different aryl groups on the 2- and 1-position of the cyclopropane ring (entries 2–5). High regioselectivity (>20:1) was observed in all cases. The selective formation of cyclobutenes with a 1,3-diaryl over 1,2-diaryl relationship may be due to steric interactions between the two aryl groups during the ring expansion. Alkyl groups could also be tolerated on the 2-position of cyclopropanes (entry 6).

In addition to hydrolysis, imine intermediate **15c** could also be reduced in-situ to form sulfonamide **16** (Table 2). The chirality in cyclopropane **4a** was also successfully transferred to the product (entry 1). This paved the way for enantioselective synthesis of four-membered rings from chiral alkynyl cyclopropanes. Commercially available cyclopropyl acetylene **4g** could be converted to sulfonamide **16g** in 85% yield (entry 2). Alkyl substituent on the 1-position of cyclopropane could also be tolerated (entry 3). We found that the cyclobutenyl aldehyde derived from acetylene **4i** was not very stable at room temperature. Direct reduction of the imine intermediate afforded stable sulfonamide **16i** in good yield and high regioselectivity (entry 4). Substrate **4j** with an alkyl group on the 1-position and aryl group on the 2-position of the cyclopropane also worked well (entry 5).

In summary, we have developed an efficient method for the preparation of highly substituted cyclobutenes from alkynyl cyclopropanes selectively. The tandem process was facilitated by a dual catalyst system (CuTc and AgOTf). This new protocol eliminated the need of isolating diazo or triazole intermediates. Various cyclobutenes with aldehyde or sulfonamide functionality could be prepared. The synthesis of cyclobutenes is greatly simplified by using *N*-sulfonyl-1,2,3-triazoles as the carbene precursor for cyclopropanation of alkene and ring expansion of cyclopropanes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

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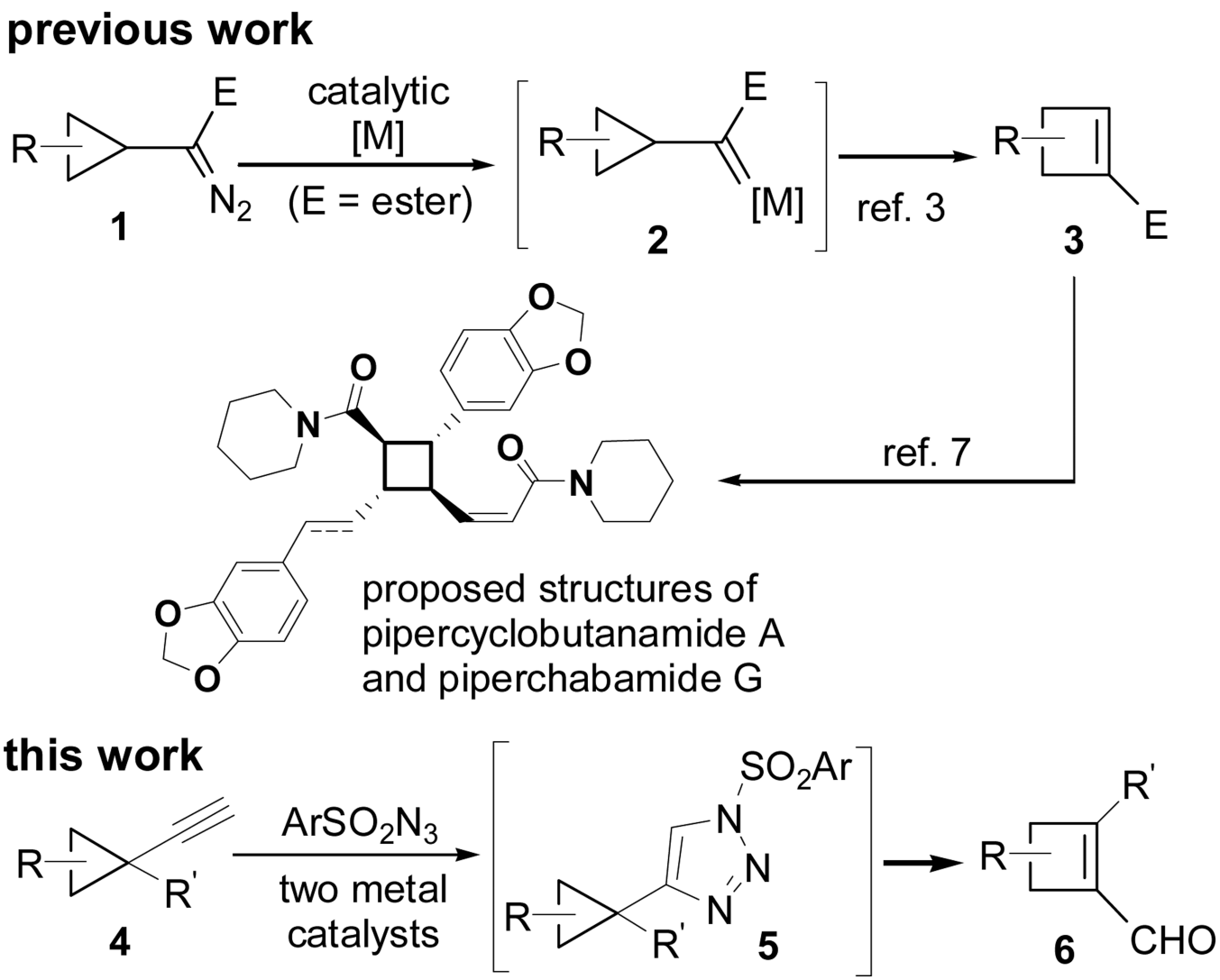
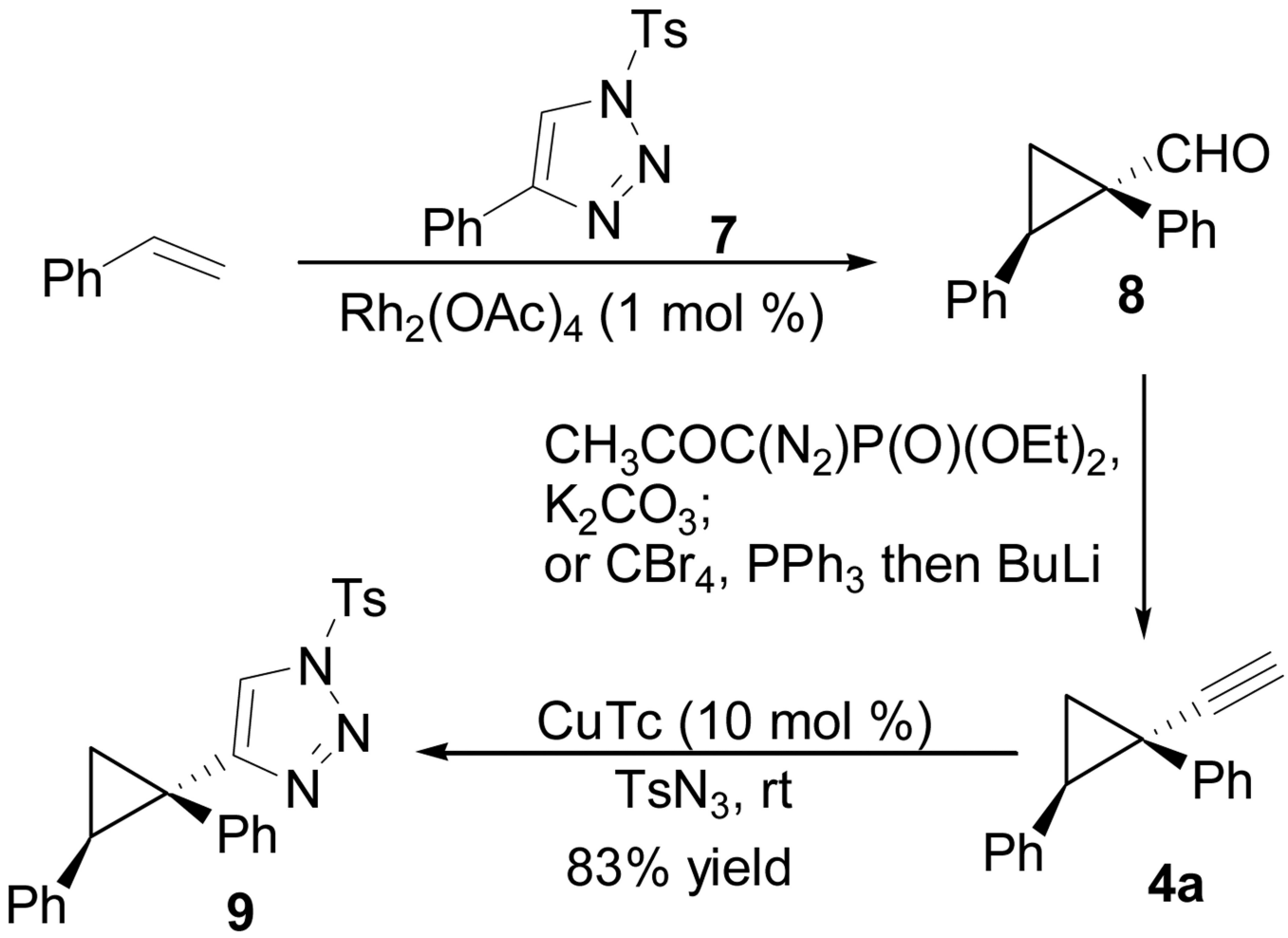
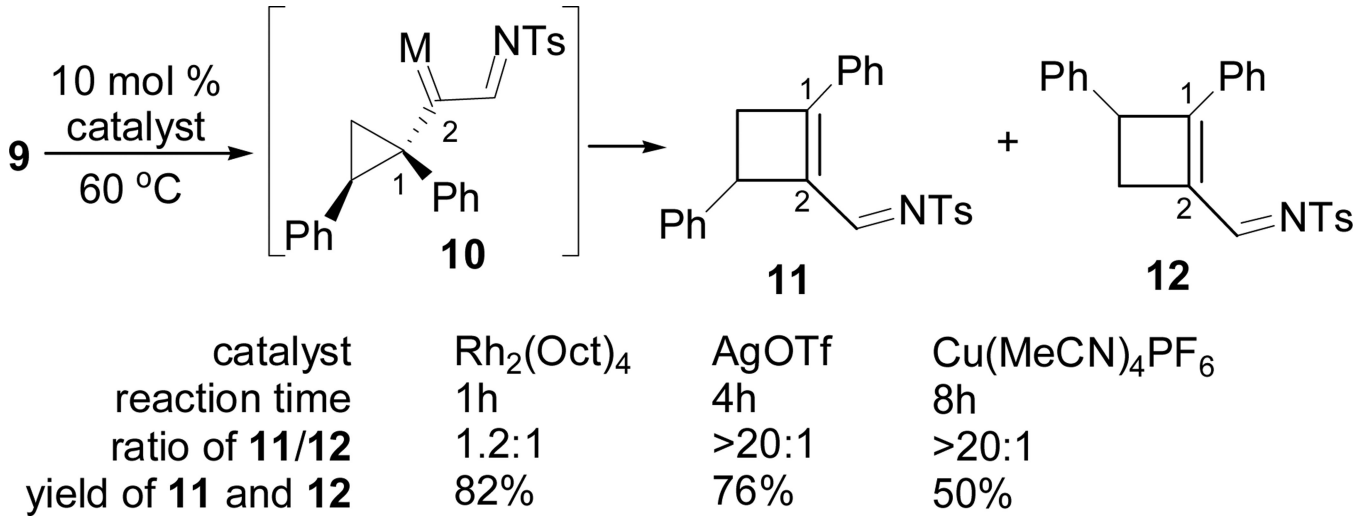


Scheme 1.
Ring Expansion of Cyclopropyl Metal Carbene

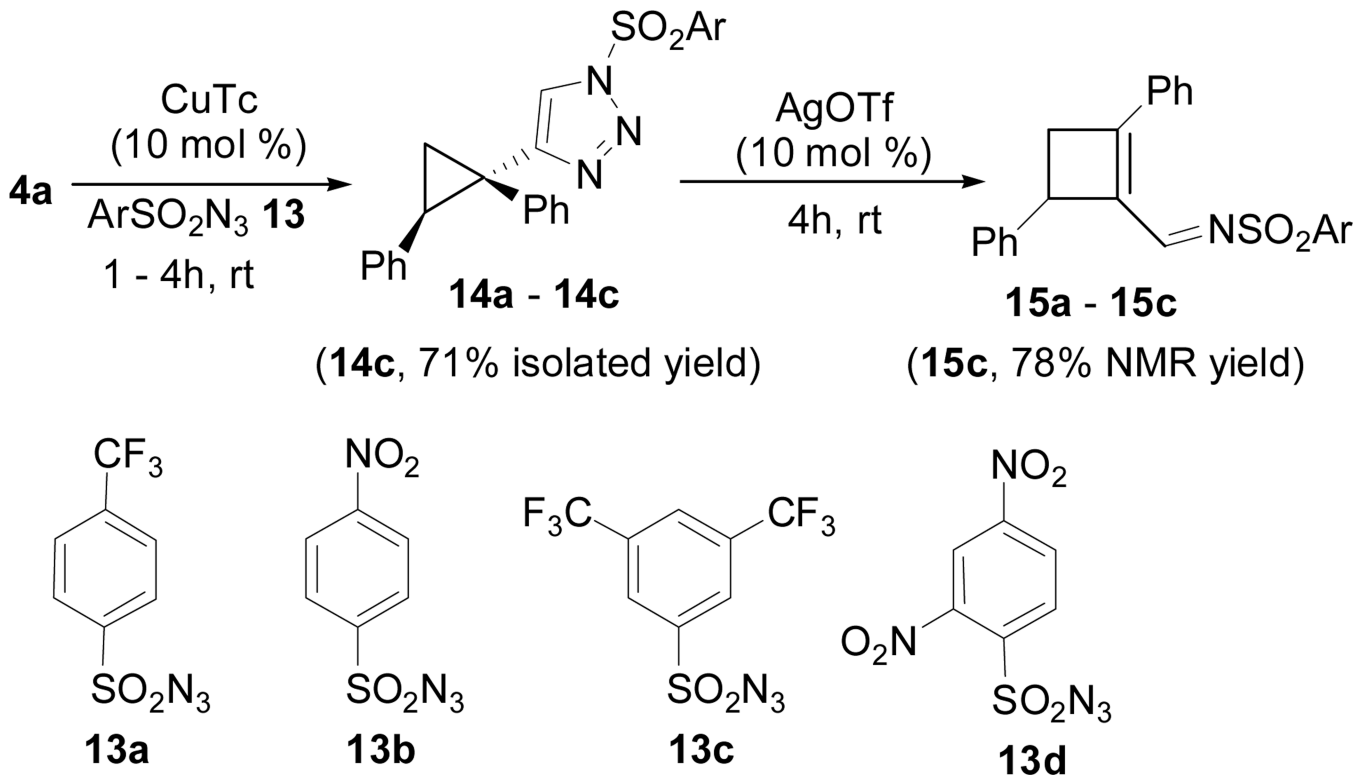


Scheme 2.
Preparation of Substituted Cyclopropanes from Alkenes



catalyst	$Rh_2(Oct)_4$	AgOTf	$Cu(MeCN)_4PF_6$
reaction time	1h	4h	8h
ratio of **11**/**12**	1.2:1	>20:1	>20:1
yield of **11** and **12**	82%	76%	50%

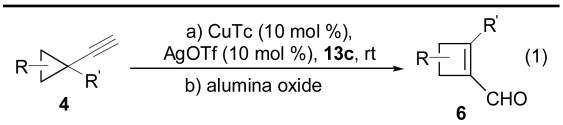
Scheme 3.
Effect of Catalysts on the Regioselectivity of Ring Expansion



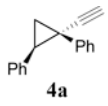
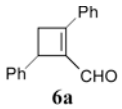
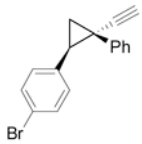
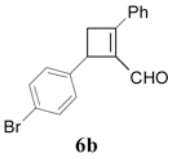
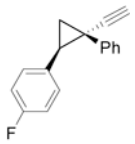
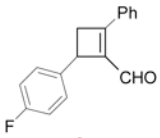
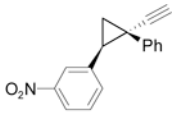
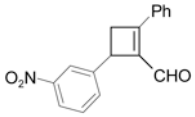
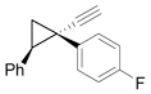
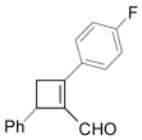
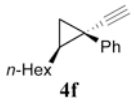
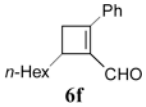
Scheme 4.
Effect of Azides on Ring Expansion

Table 1

Synthesis of Cyclobutene Aldehydes **6** from Alkynyl cyclopropanes[a]



4 **6**

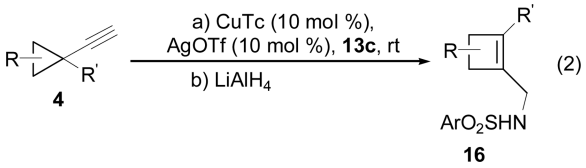
Entry	Substrate	Product[b]	Yield
1	 **4a**	 **6a**	85%
2	 **4b**	 **6b**	80%
3	 **4c**	 **6c**	80%
4	 **4d**	 **6d**	73%
5	 **4e**	 **6e**	82%
6	 **4f**	 **6f**	86%

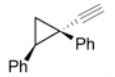
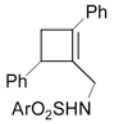
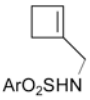
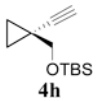
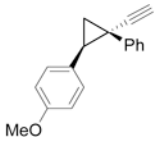
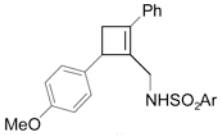
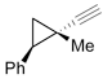
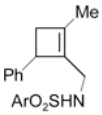
[a] Conditions: 1) CuTc (10 mol %), AgOTf (10 mol %), **13c** (1 equivalent), rt, 4-8h; 2) alumina oxide;

[b] Regioselectivity (>20:1) was determined by ^{1}H NMR of the crude product.

Table 2

Synthesis of Cyclobutene Sulfonamides **16** from Alkynyl Cyclopropanes (Ar = 3,5-$(CF_3)_2C_6H_3$)[a]



Entry	Substrate	Product[b]	Yield
1	 **4a** (81% *ee*)[c]	 **16a** (80% *ee*)	81%
2	 **4g**	 **16g**	85%
3	 **4h**	 **16h**	80%
4		 **16i**	78%
5	 **4j**	 **6j**	76%

[a]Conditions: CuTc (10 mol %), AgOTf (10 mol %), **13c** (1 equivalent), rt, 1-8h; 2) $LiAlH_4$;

[b]Regioselectivity (>20:1) was determined by ^1H NMR of the crude product.

[c]This is based on the *ee* of the aldehyde precursor.