Homogeneous Catalysis

DOI: 10.1002/anie.201201060

Enantioselective 5-*endo*-dig Carbocyclization of β-Ketoesters with Internal Alkynes Employing a Four-Component Catalyst System**

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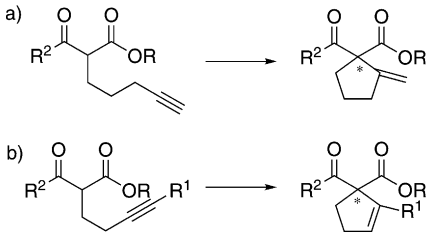
The Conia-ene reaction of acetylenic β-dicarbonyl compounds represents one of the most direct methods for the formation of carbocycles,[1] and is particularly attractive for the preparation of cyclopentane derivatives. Although the classical method of the Conia-ene reaction has some limitations in its application because of the harsh experimental conditions[1,2] such as high temperature, strong base, strong acid, or photochemical activation, recent advances in the use of transition-metal catalysis[3] and organocatalysis[4] have dramatically expanded the diversity of this reaction. In 2005, the first enantioselective intramolecular Conia-ene reaction of β-ketoesters was reported by Toste and co-workers using a palladium(II)/ytterbium(III) catalyst system.[5] This work brought the enantioselective Conia-ene reaction to the attention of a number of organic chemists worldwide, and two more methods have since appeared.[6] However, all the enantioselective methods are limited to the 5-*exo*-dig cyclization of β-dicarbonyl compounds with terminal alkynes. An endocyclic variant of the Conia-ene reaction, that is, 5-*endo*-dig cyclization of β-dicarbonyl compounds with internal alkynes, is still a challenge (Scheme 1), although the transition-metal-catalyzed 5-*endo*-dig addition of heteroatom nucleophiles to internal alkynes are common.[7]

In 2004, Toste and co-workers achieved a rare example of the gold(I)-catalyzed 5-*endo*-dig carbocyclization of 1,3-dicarbonyl compounds with internal alkynes to provide cyclopentene adducts in high yields.[8] They surveyed several cationic group 11 metal triflates including copper(I) and silver(I) triflates as catalysts for the cyclization of β-ketoesters with internal alkynyl substituents, but only triphenylphosphine/gold(I) triflate gave the desired cyclization products. The gold(I)-catalyzed 5-*endo*-dig carbocyclization reported by Toste and co-workers is amenable to a wide range of β-ketoesters having an alkynyl unit, however, the corresponding asymmetric variants are difficult and give racemic products.[5] Meanwhile, we have been engaged for several years in the development of enantioselective α-functionalization of β-dicarbonyl compounds as represented by enantioselective fluorination and hydroxylation reactions using nickel(II), zinc(II), or copper(II) complexes with a chiral 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX-Ph) or a 2,2′-isopropylidinebis(4-phenyl-2-oxazoline) (Box-Ph) ligand.[9,10] As a part of this research program for the metal-catalyzed enantioselective functionalization of 1,3-dicarbonyls, we started to investigate the enantioselective 5-*endo*-dig cyclization of β-dicarbonyl compounds with internal alkynes. Before the completion of our work, a single example of an enantioselective 5-*endo*-dig cyclization of a substrate bearing an internal alkyne was reported (65% yield with 52% *ee*) in a paper focusing on an asymmetric exocyclic Conia-ene reaction of β-dicarbonyl compounds using a La/Ag heterobimetallic catalyst.[6b] On the basis of the work by Toste and co-workers, Sanz and co-workers recently devised an enantioselective 5-*endo*-dig gold(I)-catalyzed cycloisomerization of *o*-(alkynyl)styrenes,[6c] however, their achievement could not be applied for the target enantioselctive endocyclic variant of the Conia-ene reaction using 1,3-dicarbonyl compounds. Just before the submission of this manuscript, the group of Toste achieved a unique enantioselective transition-metal-catalyzed cyclization of use of silyloxyenyens, and not β-ketoesters, using chiral phosphine ligands.[11] We report herein the first achievement of a 5-*endo*-dig cyclization of β-dicarbonyl compounds having internal alkynes by employing the four-component system Box-Ph/Zn^{II}/$Yb(OTf)_3$/HFIP (HFIP = hexafluoroisopropyl alcohol) to deliver products in high yields and with enantioselectivities of up to 98% *ee*.



Scheme 1. Enantioselective carbocyclization. a) 5-*Exo*-dig cyclization of β-dicarbonyl compounds with terminal alkynes (known). b) The 5-*endo*-dig cyclization of β-dicarbonyl compounds with internal alkynes (challenge).

We envisioned that novel catalytic access to enantioselective 5-*endo*-dig cyclization of β-dicarbonyl compounds with internal alkynes **1** should be feasible by the proper

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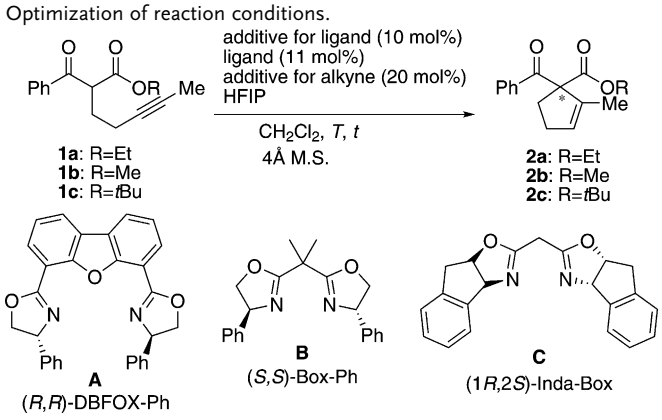
[**] This study was financially supported in part by Grants-in-Aid for Scientific Research (21390030, 22106515, Project No. 2105: Organic Synthesis Based on Reaction Integration). We also thank TOSOH F-TECH INC., and the Asahi Glass Foundation for support in part. E.T. acknowledges Grants-in-Aid for Scientific Research for financial support (23915014).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201060.

selection of soft Lewis acids for alkyne activation and metal(II) salts for the two-point binding of dicarbonyl compounds with chiral ligands. To begin with, we simply attempted the intramolecular addition of a β-ketoester to an internal alkyne under the reaction conditions for endocyclization[8] (Table 1, entry 1), Conia-ene *exo* cyclization[3h,5] (entry 2), and fluorination and hydroxylation reactions[10] (entries 3 and 4) in the presence of the DBFOX-Ph ligand (**A**). All the reactions, however, did not proceed even after 3 days at room temperature. These results implied that the DBFOX-Ph ligand inhibits both gold/silver- and ytterbium-catalyzed intramolecular cyclization (entries 1 and 2), and the alkyne moiety of **1a** could not be activated by either the Zn^{II}/DBFOX-Ph or Ni^{II}/DBFOX-Ph complex (entries 3 and 4).

Table 1: The 5-*endo*-dig cyclization of β-ketoesters with internal alkynes: Optimization of reaction conditions.



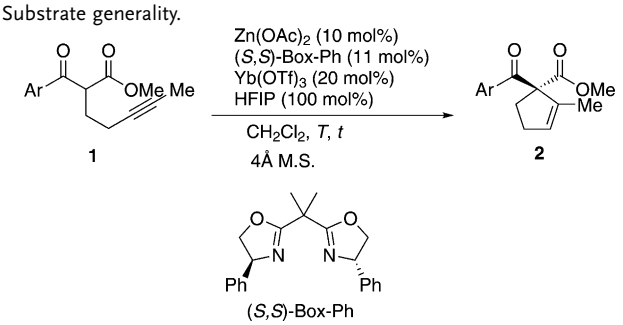
	1	Ligand	Additive for ligand	Additive for alkyne	HFIP [mol%]	T [°C]	t [d]	Yield [%][a]	ee [%][b]
1	**1a**	**A**	–	AgOTf/[Au(PPh$_3$)Cl]	–	RT	3	n.r.	–
2	**1a**	**A**	–	Yb(OTf)$_3$	–	RT	3	n.r.	–
3	**1a**	**A**	Ni(ClO$_4$)$_2$/6H$_2$O	–	–	RT	3	n.r.	–
4	**1a**	**A**	Zn(OAc)$_2$	–	–	RT	3	n.r.	–
5	**1a**	**A**	Ni(ClO$_4$)$_2$/6H$_2$O	Yb(OTf)$_3$	–	RT	3	n.r.	–
6	**1a**	**A**	Zn(OAc)$_2$	Yb(OTf)$_3$	–	RT	3	90	12
7	**1a**	**A**	Zn(OAc)$_2$	Sc(OTf)$_3$	–	RT	3	91	0
8	**1a**	**A**	ZnCl$_2$	Sc(OTf)$_3$	–	RT	3	85	3
9	**1a**	**A**	Mg(OTf)$_2$	Yb(OTf)$_3$	–	RT	3	n.r.	–
10	**1a**	**A**	Zn(OAc)$_2$	Yb(OTf)$_3$	100	RT	1	90	35
11	**1a**	**A**	Zn(ClO$_4$)$_2$/6H$_2$O	Yb(OTf)$_3$	100	RT	2	92	30
12	**1a**	**A**	Zn(NTf$_2$)$_2$	Yb(OTf)$_3$	100	RT	3	80	29
13	**1a**	**B**	Zn(OAc)$_2$	Yb(OTf)$_3$	100	0	2	61	84
14	**1b**	**B**	Zn(OAc)$_2$	Yb(OTf)$_3$	100	0	2.5	70	90
15	**1c**	**B**	Zn(OAc)$_2$	Yb(OTf)$_3$	100	0	3	22	73
16	**1b**	**C**	Zn(OAc)$_2$	Yb(OTf)$_3$	100	0	2	10	67
17	**1b**	**B**	Zn(OAc)$_2$	Yb(OTf)$_3$	50	0	2.5	51	86
18	**1b**	**B**	Zn(OAc)$_2$	Yb(OTf)$_3$	100[c]	0	2.5	65	89
19	**1b**	**B**	Zn(OAc)$_2$	Yb(OTf)$_3$	100[d]	0	2	70	62
20	**1b**	**B**	Zn(OAc)$_2$	Yb(OTf)$_3$	100[e]	0	1.5	72	75

Unless stated otherwise, see the Supporting Information for details of the reaction conditions. [a] Yield of isolated product. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Phenol was used instead of HFIP. [d] *i*PrOH was used instead of HFIP. [e] CF_3CH_2OH was used instead of HFIP. M.S. = molecular sieves, Tf = trifluoromethansesulfonyl.

We next examined the reaction of **1a** using a combination of reaction conditions (entries 5–9). While no reaction was observed using either Ni^{II}/Yb(OTf)$_3$/DBFOX-Ph or Mg^{II}/Yb(OTf)$_3$/DBFOX-Ph at room temperature (entries 5 and 9), we were pleased to find that the desired *endo*-cyclized product **2a** was obtained in excellent yield (90%) by the combination of Zn^{II}/DBFOX-Ph and either Yb(OTf)$_3$ or Sc(OTf)$_3$ after stirring for 3 days at room temperature; the product however was nearly racemic (entries 6–8). Much to our delight, the addition of HFIP[10f] to the above reaction conditions resulted in the desired enantioenriched **2a** with 29–35% *ee* (entries 10–12). DBFOX-Ph, a useful chiral ligand for the α-functionalization of β-ketoesters in our earlier studies, did not lead to high enantioselectivity in the current work. This poor enantioselectivity is perhaps due to the highly rigid structure of the substrate/metal(II)/DBFOX-Ph complex, which should be disadvantageous for an intramolecular cyclization involving ring strain. We therefore focused on a more flexible chiral ligand, (*S*,*S*)-Box-Ph (**B**). Indeed, in our early work for enantioselective fluorination, we learned that the there was greater flexibility in the metal complex of the Box-Ph ligand than for DBFOX-Ph. Either of the two enantiomers of the products were obtained enantioselectively by a simple change of the metal salt, from copper(II) to nickel(II), without any change in the chirality of the Box-Ph ligand used.[9] The origin of the reversed sense of stereoinduction is a consequence of a change in the geometry of the metal center from distorted square planar to square pyramidal in the transition state. Thus the Box-Ph ligand tends to be flexibly bent depending upon the character of metal salts used as well as substrates.[12] As expected, the enantioselectivity here perceptibly increased from 35% to 84% *ee* when using Box-Ph instead of DBFOX-Ph as the ligand for the zinc(II) catalyst (entry 13). Additional improvement of the enantioselectivity to 90% *ee* was observed when the substrate was changed from the ethyl ester **1a** to the methyl ester **1b** (entry 14). In contrast, the enantioselectivity decreased with the *tert*-butyl ester **1c** (73% *ee*, entry 15). These results clearly indicate that the size of the ester moiety plays a critical role in its chiral induction. When Inda-Box (**C**) was used as a ligand, both the yield and enantioselectivity of **2b** decreased to 10% and 67% *ee*, respectively (entry 16). It is also noteworthy that the degree of enantioselectivity appears not to be proportional to the amount of HFIP employed. Thus, when the amount of HFIP used was reduced by a half, the enantioselectivity of the reaction was found to depreciate only slightly (entry 14 versus 17). Hence, a proper amount of HFIP is critical to obtaining high enantioselectivity. Interestingly, HFIP can be replaced by phenol, the acidity of which is nearly the same as that of HFIP (pK_a values around 9; entry 18). Other additives such as *i*PrOH and trifluoroethanol also afforded **2b**, but the enantioselectivities were moderate to good (entries 19 and 20). The screening of more additives (Et_3SiOTf, pentafluorophenol, acetic acid, etc.,) did not result in an improved enantioselectivity for **2** (see Table S1 in the Supporting Information). Hence, the four-component system of Zn(OAc)$_2$/Yb(OTf)$_3$/Box-Ph/HFIP became the choice catalyst system for the enantioselective 5-*endo*-dig cyclization of β-dicarbonyl compounds with internal alkynes **1**.

Having obtained an optimized protocol for catalytic enantioselective 5-*endo*-dig cyclization, we next evaluated the scope of the substrate (Table 2). This catalytic system is quite general for a wide range of β-ketoesters **1**. The results summarized in Table 2 indicate that substituents on the aryl group as well as their position had little effect on the yield and enantioselectivity of the reaction (entries 1–11). For example,

Table 2: The 5-*endo*-dig cyclization of β-ketoesters with internal alkynes: Substrate generality.

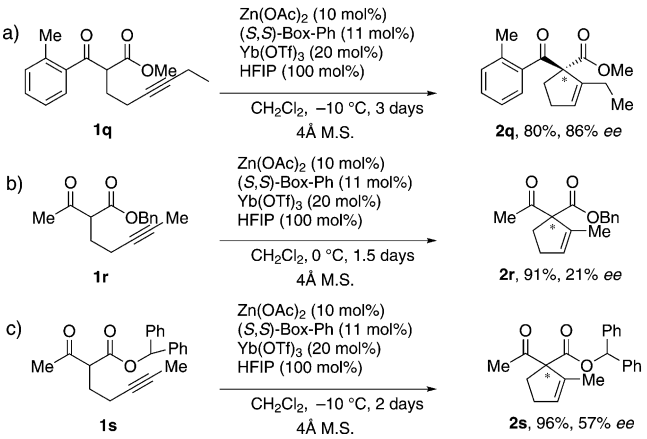


Entry	**1**	Ar	*T* [°C]	*t* [d]	**2**	Yield [%][a]	*ee* [%][b]
1	**1b**	Ph	0	2.5	**2b**	70	90
2	**1d**	2-MeC_6H_4	−10	2	**2d**	99	95
3	**1e**	3-MeC_6H_4	−10	2.5	**2e**	91	88
4	**1f**	4-MeC_6H_4	0	2	**2f**	95	78
5	**1g**	2-$MeOC_6H_4$	−10	2	**2g**	99	94
6	**1h**	3-$MeOC_6H_4$	−10	2.5	**2h**	95	90
7	**1i**	2,6-$MeOC_6H_3$	−10	2	**2i**	75	93
8	**1j**	2-FC_6H_4	−10	2	**2j**	94	92
9	**1k**	2-ClC_6H_4	−10	2	**2k**	98	96
10	**1l**	2-BrC_6H_4	−10	2	**2l**	93	98
11	**1m**	2-IC_6H_4	−10	1	**2m**	75	93
12	**1n**	1-Naphthyl	−10	2	**2n**	97	95
13	**1o**	2-Naphthyl	−10	4	**2o**	91	95
14[c]	**1o**	2-Naphthyl	−10	4	**2o**	93	90
15	**1p**	6-Br-2-Naphthyl	−10	2	**2p**	88	82

Unless stated otherwise, see the Supporting Information for details of the reaction conditions. [a] Yield of isolated product. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Phenol was used instead of HFIP.

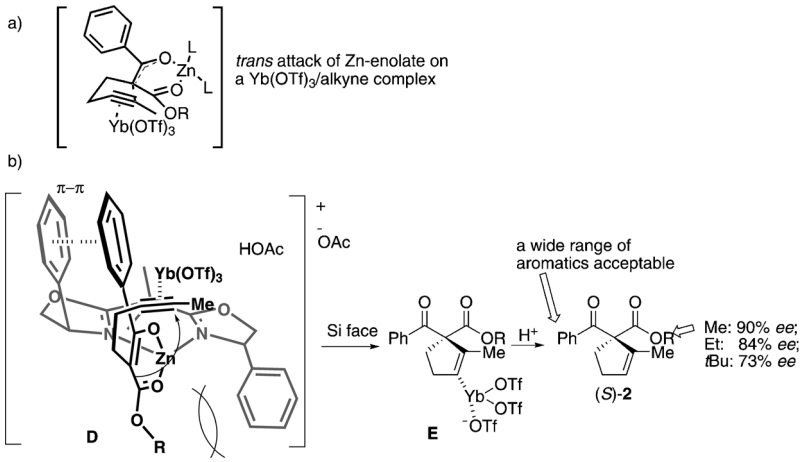
substrates having a methyl group at either the *ortho*, *meta*, or *para* position of the benzene ring were found to be workable substrates in the 5-*endo*-dig cyclization, thus affording high yields of **2d–f** with high enantioselectivities (entries 2–4). Aryl groups with methoxy (**1g–i**) or halogen substitutents (fluoro, chloro, bromo, and iodo; **1j–m**) also afforded the products **2g–m** in high yields with high enantioselectivities (entries 5–11). The reactions of the large aromatic 1- or 2-naphthyl substrates **1n–p** also gave the desired products **2n–p** in excellent yields with high enantioselectivities (entries 12–15). Phenol was also an effective additive for this transformation and provided **2o** in 93% yield with 90% *ee*, although the enantioselectivity was slightly worse than that obtained when using HFIP (entries 13 and 14). All the reactions proceeded quite well and in all cases no *exo* cyclization was observed. The absolute configuration of the newly generated spiro center of **2** was unequivocally determined by X-ray crystallography of **2p**,[13] which showed the stereogenic carbon centre formed to be of *S* stereochemistry (see Figure S1 in the Supporting Information). The configurations of other spiro products **2** were assigned on the basis of an assumption that those cyclizations operate by a similar mechanism and hence have similar facial selectivity.

To explore the limitation of the present method, and also to obtain mechanistic information on this enantioselective reaction, three different types of β-ketoesters, **1q–s**, were used as substrates for this cyclization reaction. Under the same reaction conditions, the dicarbonyl compound **1q** having a terminal ethyl ethynyl group participated to afford **2q** in 80% with 86% *ee* (Scheme 2a). The reaction of the aliphatic β-ketoester **1r** also proceeded nicely to furnish product **2r** in high yield (91%), but the enantioselectivity was poor (21% *ee*; Scheme 2b). This lack of enantiocontrol for nonaromatic substrates seems to be a limitation of the present method, but the low enantioselectivity was improved to 57% *ee* when the bulky benzhydryl ester **1s** was used (Scheme 2c).



Scheme 2. Exploring the limitations of the reaction: Enantioselective 5-*endo*-dig cyclization of β-dicarbonyl compounds with internal alkynes.

On the basis of the absolute configuration of products **2**, and in light of the reported X-ray structure of the Zn^{II}/(*S*,*S*)-Box-Ph complex,[12] as well as the experimental data shown in Tables 1, and 2, and Scheme 2, we assumed a complex such as **D** for Zn^{II}/Box-Ph/**1**, as shown in Scheme 3. The complex **D** is close to a tetrahedral geometry at the zinc metal. The two phenyl substituents in Zn^{II}/Box-Ph are arranged perpendicular to each other. More importantly, they are positioned pseudoaxially and pseudoequatorially to the left and right, respectively. The pseudoaxially positioned left phenyl substituent is parallel to the aromatic moiety of the substrates **1** and thus it could perhaps be stabilized in part through a π–π stacking interaction. This arrangement could be the reason for the success of the aromatic ketones **1a–q** independent of their bulkiness, and the low enantioselectivity of the nonaromatic ketone **1r** could be explained by the lack of corresponding π–π stacking interactions in the transition state. Intramolecular nucleophilic *trans* attack[8] of the zinc enolate on an $Yb(OTf)_3$/alkyne complex (Scheme 3a) could afford a ytterbium intermediate **E**, which is protonated to give product (*S*)-**2**. Although the activation of alkynes by Yb-

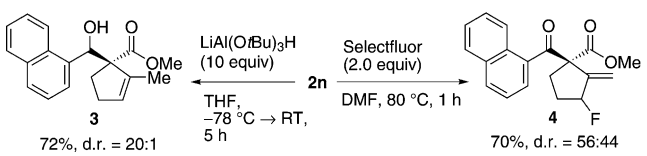


Scheme 3. Reaction mechanism: Proposed transition-state model leading to (*S*)-**2**.

$(OTf)_3$ has been proposed, we could not detect the intermediate **D** complexed with $Yb(OTf)_n$ using LC/MS spectroscopy. This result indicates the carbon–Yb bond is too weak to be protonated rapidly. In the complex **D**, the Re face of the zinc enolate **1** is perfectly shielded by the phenyl group, of the (*S*,*S*)-Box-Ph ligand, on the left so that the appended internal alkyne approaches from the Si face of the zinc enolate (Scheme 3b). In contrast, the phenyl group on right is perpendicular to the plane of the six-membered zinc enolate of **1**.[12] Therefore, the enantioselectivity of **2** tends to be slightly decreased with the increase of the ester size by steric repulsion (see Table 1, entries 13–15). The effect of HFIP is presumably to improve the catalytic turnover by protonation of a zinc–oxygen bond and subsequent release of the products from the transition state (i.e., from **D** to **E**), or assist in the enolization of **1**, or assist in the final protonation of **E**.[10f] The enantioselection observed is essentially the same even in the absence of HFIP and use of other additives such as PhOH and *i*PrOH, although further studies are required. No 5-*exo*-dig cyclization product was observed because of its highly strained four-membered structure.

Finally, transformations of the 5-*endo*-dig cyclization products **2** were attempted. Diastereoselective reduction of **2n** proceeded quite nicely by the use of $LiAl(OtBu)_3H$[10e] to provide the alcohol **3** in high yield with an excellent diastereoselectivity of 20:1. Isomerization by fluorination of **2n** with Selectfluor in DMF[14] was also possible to provide the medicinally attractive allylic fluoride **4** in 70% yield (Scheme 4).[15]

In conclusion, we have developed the catalytic enantioselective 5-*endo*-dig cyclization of β-ketoesters **1** having an internal alkyne. High enantioselectivity was achieved by the use of the four-component system Zn^{II}/(*S*,*S*)-Box-Ph/Yb-$(OTf)_3$/HFIP, which provides an effective entry to medicinally attractive chiral spiro cyclopentene compounds. The keys for the success of this reaction are the flexibility of chiral the Box-Ph ligand, the proper combination of metal salts for the ligand and for alkyne activation, and the presence of HFIP. As is mentioned in the introduction, a single example of enantioselective 5-*endo*-dig cyclization of β-ketoesters with internal alkynes was reported just before the completion of this work, but the enantioselectivity is not satisfactory.[6b] Therefore this is the first practical method for a 5-*endo*-dig variant of the Conia-ene carbocyclization. The limitation of the present methodology lies with the substrates having nonaromatic ketones such as **1r** (Scheme 2b), and it can be overcome by the proper choice in the sterically demanding ester unit in the substrates; and in such a case, the reaction mechanism should be different from the present case. Additional work in this area and the application of this four-component system to other cyclizations including a conventional enantioselective 5-*exo*-dig Conia-ene reaction, as well as their application to natural product synthesis is in progress and will be reported at a later date.



Scheme 4. Transformations: Reduction or fluorination of **2n**.

Received: February 8, 2012
Published online: March 15, 2012

Keywords: alkynes · cyclizations · enantioselectivity · fluorine · Lewis acids

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