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Thermal Intramolecular [4 + 2] Cycloadditions of Allenamides: A Stereoselective Tandem Propargyl Amide Isomerization−Cycloaddition

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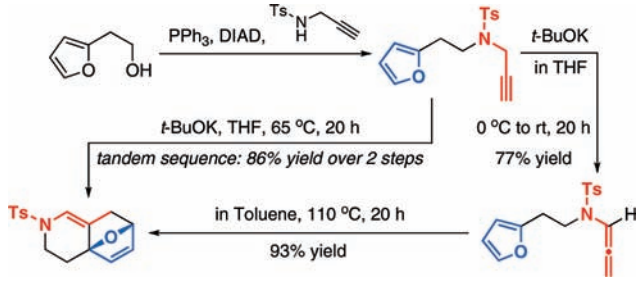
ABSTRACT



A stereoselective intramolecular normal demand [4 + 2] cycloaddition of allenamides under thermal conditions without metal assistance is described. This work led to the development of a stereoselective tandem propargyl amide-isomerization−[4 + 2] cycloaddition sequence amenable for rapid assembly of complex nitrogen heterocycles.

We have been embarking on the chemistry of allenamides over the past 10 years.[1,2] In particular, allenamides have proven to be an excellent source of nitrogen-stabilized oxyallyl cations[3,4] through DMDO-epoxidation, thereby allowing us to develop highly stereoselective [4 + 3] cycloaddition manifolds[5−7] including intramolecular[8,9] cycloadditions such as using *N*-tethered allenamide **1**[9] en route

(1) For a review on the chemistry of allenamides, see: Hsung, R. P.; Wei, L.-L.; Xiong, H. *Acc. Chem. Res.* **2003**, *36*, 773.

(2) For recent reports on allenamide chemistry, see: (a) Hayashi, R.; Hsung, R. P.; Feltenberger, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125. (b) Skucas, E.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 5054. (c) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2009**, *11*, 1547. (d) Beccalli, E. M.; Broggini, G.; Clerici, F.; Galli, S.; Kammerer, C.; Rigamonti, M.; Sottocornola, S. *Org. Lett.* **2009**, *11*, 1563. (e) Broggini, G.; Galli, S.; Rigamonti, M.; Sottocornola, S.; Zecchi, G. *Tetrahedron Lett.* **2009**, *50*, 1447. (f) Brummond, K. M.; Yan, B. *Synlett* **2008**, 2303. (g) Fuwa, H.; Tako, T.; Ebine, M.; Sasaki, M. *Chem. Lett.* **2008**, *37*, 904. (h) González-Gómez, A.; Añorbe, L.; Poblador, A.; Domínguez, G.; Pérez-Castells, J. *Eur. J. Org. Chem.* **2008**, 1370.

(3) For excellent reviews on heteroatom-substituted oxyallyl cations in [4 + 3] cycloadditions, see:(a) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297. (b) Harmata, M. *Rec. Res. Dev. Org. Chem.* **1997**, *1*, 523.

(4) For leading examples of nitrogen-stabilized oxyallyl cations in [4 + 3] cycloadditions, see: (a) MaGee, D. I.; Godineau, E.; Thornton, P. D.; Walters, M. A.; Sponholtz, D. J. *Eur. J. Org. Chem.* **2006**, 3667. (b) Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001**, *3*, 425. (c) Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett.* **1999**, *1*, 2017. (d) Dennis, N.; Ibrahim, B.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans.* **1976**, *1*, 2307.

(5) For our nitrogen-stabilized oxyallyl cations in intermolecular [4 + 3] cycloadditions with furans and pyrroles, see: (a) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174. (b) Antoline, J. E.; Hsung, R. P.; Huang, J.; Song, Z.; Li, G. *Org. Lett.* **2007**, *9*, 1275. (c) Antoline, J. E.; Hsung, R. P. *Synlett* **2008**, 739.

(6) For our asymmetric [4 + 3] cycloadditions, see Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50.

(7) Also see :(a) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058. (b) For an enantioselective formal [4 + 3] cycloaddition, see: Dai, X.; Davies, H. M. L. *Adv. Synth. Catal.* **2006**, *348*, 2449.

(8) For intramolecular [4 + 3] cycloadditions of *C*-tethered allenamides, see: Rameshkumar, C.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 615.

(9) For intramolecular [4 + 3] cycloadditions of *N*-tethered allenamides, see: Xiong, H.; Huang, J.; Ghosh, S.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694.

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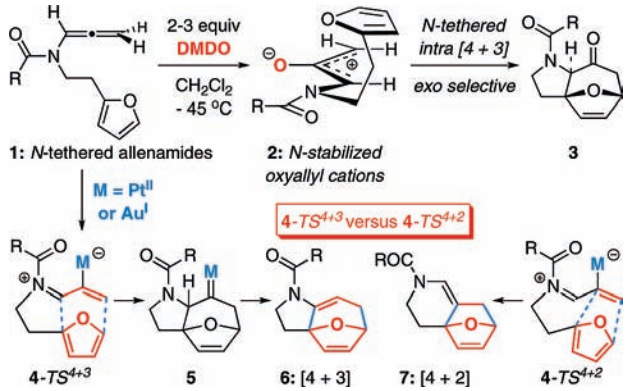
to synthetically useful nitrogen heterocycle **3** (Scheme 1). However, the dependence on DMDO as the key oxidant for

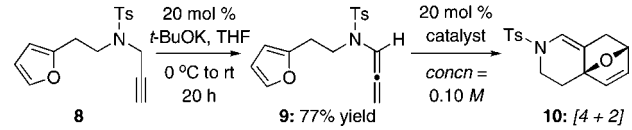
Scheme 1. Cycloadditions of *N*-Tethered Allenamides



the transformation can pose a challenge in terms of scale and operational convenience. Mascareñas's report[10] intrigued us because of their usage of $PtCl_2$/CO in catalyzing a [4 + 3] cycloaddition of allenes. More significantly, they also documented that a different catalyst [AuCl] could effectively direct the reactivity toward the competing [4 + 2] cycloaddition instead of the [4 + 3] cycloaddition. Recently, Toste[11] revealed a similar divergence in [4 + 2] versus [4 + 3] cycloaddition when using different ligands along with a Au(I) catalyst. Our own efforts in exploring Mascareñas's $PtCl_2$ versus AuCl protocol[10,12,13] while adopting allenamides led us to an interesting and different direction than the initially anticipated issues regarding competing [4 + 3] and [4 + 2] cycloadditions (see **4**-TS^{4+3} → **6** vs **4**-TS^{4+2} → **7**, respectively, in Scheme 1). We report here a rare normal electron-demand[1,14−17] [4 + 2] cycloaddition involving electron-rich heteroatom-substituted allenes under thermal conditions and a stereoselective tandem propargyl amide isomerization−intramolecular [4 + 2] cycloaddition sequence.

To commence our studies, we initially examined an *N*-Boc-substituted allenamide, but it was not useful for platinum and gold protocols (see ref 18 for results). Consequently, *N*-sulfonyl-allenamide **9**[19] was prepared from propargyl amide **8** via our base-promoted isomerization protocol using catalytic *t*-BuOK.[20] We quickly found that with the exception of AuCl (entries 5−7 in Table 1), platinum catalysts (entries 1−4), and Au(III) catalyst (entry 9) were not useful in generating any cycloaddition types of products. Concentrations did not appear to have any impact, as reactions run at 0.04 M led to the same outcome.

Table 1. Exploring Conditions for the Cycloaddition



entry	catalysts	4 Å MS	solvents	temp (°C)	time	yield (%)[a]
1	$PtCl_2$	yes	DCE	65	<12 h	0
2	$PtCl_4$	yes	DCE	65	3 h	13[c]
3	$PtCl_4$	yes	THF	65	6 h	15[c]
4	$PtCl_4$	yes	toluene	23	1 h	11[c]
5	AuCl	yes	DCE[b]	23	10 min	66
6	AuCl	yes	THF	65	6 h	35[c]
7	AuCl	yes	toluene	65	<30 min	42[c]
8	AuCl/$AgSbF_6$	yes	DCE	23	1 h	16[c]
9	$AuCl_3$	yes	DCE	65	10 min	0
10	$AgSbF_6$	yes	DCE	65	6 h	85[c]
11	$AgBF_4$	yes	DCE	65	6 h	94
12	$AgBF_4$	yes	toluene	65	6 h	80[c]
13	$AgBF_4$	yes	THF	65	<12 h	57[c]
14	CSA[d]	yes	DCE	65	<12 h	92[c]
15	PPTS[d]	yes	DCE	65	8 h	94[c]
16	**no**	**yes**	**THF**	**65**	**30 h**	**91**[c]
17	**no**	**no**	**d_8-toluene**	**110**	**20 h**	**93**

[a] Isolated yields unless otherwise indicated. [b] DCE: 1,2-dichloroethane. [c] NMR yields determined with phenanthrene as the internal standard. [d] 10 mol % was used.

Most intriguingly, the illustration of the corresponding [4 + 2] cycloadduct **10** shown in Table 1 has the benefit of hindsight after a series of subsequent studies. As shown in Figure 1, although **10** and its regioisomer **11** are readily distinguishable, it is not obvious how to unambiguously

(10) For a recent account on intramolecular [4 + 3] cycloadditions of allenes using $PtCl_2$, see: Trillo, B.; López, F.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2007**, *47*, 951. (b) Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *Chem.—Eur. J.* **2009**, *15*, 3336.

(11) Mauleón, P.; Zeldin, R. M.; González, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348.

(12) For a leading review on this chemistry, see: Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167.

(13) For reviews on platinum and gold chemistry, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (d) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847.

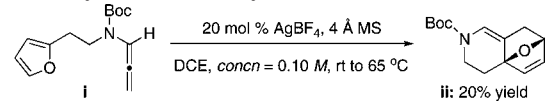
(14) For a compendium on chemistry of allenes, see: Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vols. 1 and 2.

(15) For a leading reference on normal electron-demand Diels−Alder cycloadditions of allenamides generated in situ, see: Lee, M.; Morimoto, H.; Kanematsu, K. *Tetrahedron* **1996**, *52*, 8169.

(16) For an example using *N*-allenylsulfenimide, see: Bacci, J. P.; Greenman, K. L.; van Vranken, D. L. *J. Org. Chem.* **2003**, *68*, 4955.

(17) For some examples of normal electron-demand Diels-Alder cycloadditions of allenoethers, see: (a) Hayakawa, K.; Aso, K.; Shiro, M.; Kanematsu, K. *J. Am. Chem. Soc.* **1989**, *111*, 5312. (b) Wu, H.-J.; Liu, C.-F.; Fang, Z.; Lin, H.-C. *Tetrahedron Lett.* **2007**, *48*, 6192, and references cited therein. (c) For an example of allenyl sulfides, see Yeo, S.-K.; Shiro, M.; Kanematsu, K. *J. Org. Chem.* **1994**, *59*, 1621.

(18) When utilizing a Boc-substituted allenamide (see **i**), reactions promoted by $PtCl_2$, $PtCl_4$, AuCl, or $AuCl_3$ (in 10−100 mol % at rt to 65 °C) led to very low yields of possible cycloadduct (**ii**) with mostly hydrolysis of the starting allenamide and decomposition. Only when using $AgSbF_6$ was a modest yield attained for cycloadduct **ii**.



(19) See Supporting Information.

(20) (a) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (b) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Org. Lett.* **2000**, *2*, 2869.

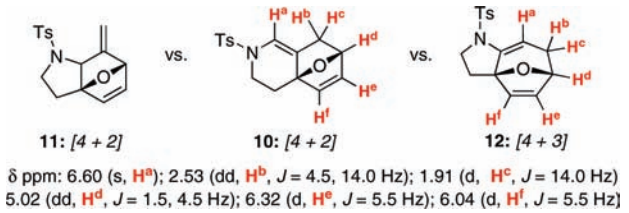


Figure 1. [4 + 2] versus [4 + 3] cycloadducts.

distinguish **10** from potential [4 + 3] cycloadduct **12** solely based on the key ^{1}H NMR resonances. However, as we continued our explorations and began to achieve high-yielding reactions with silver salts (entries 10−13), Brønsted acids (entries 14 and 15), and then ultimately simple thermal conditions with (entry 16) or without 4 Å MS (entry 17), we recognized that this did not appear to be a simple [4 + 3] cycloaddition process. Instead, it turned out to be exclusively a [4 + 2] cycloaddition pathway under all conditions after attaining an X-ray crystal structure (vide infra).

Table 2. Thermal [4 + 2] Cycloadditions of of Allenamides

entry	allenamides[a]	time [h]	cycloadducts	yield [%][b]
1	**13a:** R = *p*-Ns	12	**14a:** R = *p*-Ns	92
2	**13b:** R = Boc	20	**14b:** R = Boc	65
3	**13c:** R = (-)-menthyl	20	**14c:** R = (-)-menthyl	54[c]
4	(±)-**15a:** R = Ph	2	**16a:** R = Ph	77[d]
5	(±)-**15b:** R = Me	30	**16b:** R = Me	57[d]
6	**17**	<12	**19**	77
7	**18**	4	**20**	93
8	**21**	24	**22** / **23**	95[e]
9	**24**	20	**25**	78

[a] Unless otherwise noted, all reactions were carried out in THF at 85 °C at concn = 0.10 M. Reactions in entries 3 and 8 were run in toluene. Entries 4 and 8 were run at 45 and 110 °C, respectively. [b] Isolated yields. [c] Only one isomer by ^{1}H NMR but absolute configuration unassigned. [d] **16a** and **16b** were found as a ~3:1 inseparable isomeric mixture. [e] Regioisomeric ratio of regioisomers **22** and **23** is ~4:1.

The ability to pursue this cycloaddition thermally represents a unique opportunity for two major reasons. First, as shown in Table 2, this thermally driven allenic-[4 + 2] cycloaddition manifold possesses a much broader synthetic potential than previous work.[10,11]

The substrate scope is composed of (1) different *N*-substituents (entries 1−3) including carbamates; (2) substitutions at the allenic γ-position ((±)-**15a** and (±)-**15b** in entries 4 and 5, respectively) that gave the respective cycloadducts **16a** and **16b** with the major isomers shown as assigned via NOE experiments (Figure 2); (3) various furan substitutions

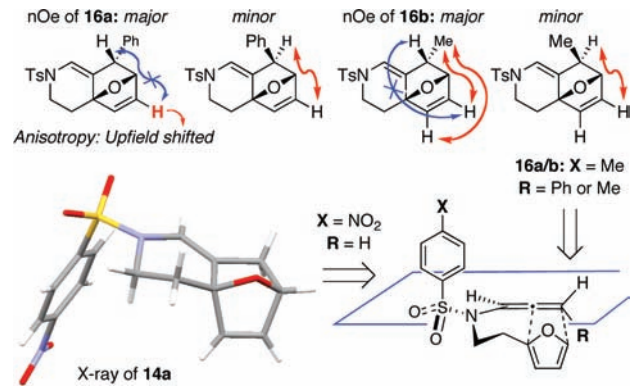
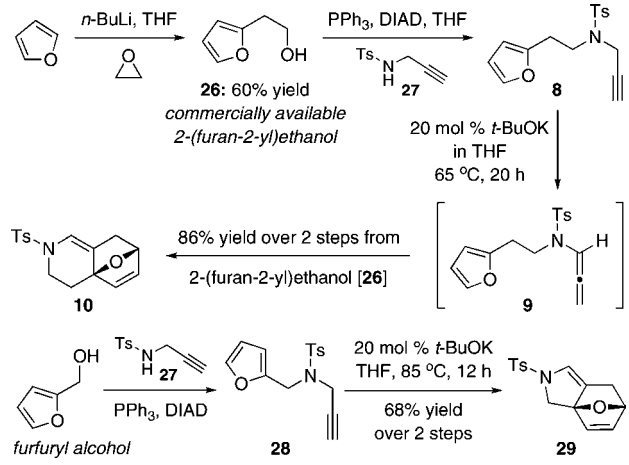


Figure 2. NOE experiments and X-ray structure of **14a**.

(entries 6 and 7); (4) a longer tethering that led to the regiochemical outcome in favor of the internal olefin of the allenic motif (**22** in entry 8), which is found as a single diastereomer,[21] and also notably in this case, when using 10 mol % of $AgBF_4$ and 4 Å MS, **22** was isolated in 58% yield as the only regioisomer after heating in toluene at 110 °C for 36 h;[21] and last, (5) a simple butadiene (entry 9).

Scheme 2. Tandem Propargyl Amide-Isomerization−[4 + 2] Cycloaddition



The X-ray structure of cycloadduct **14a** unambiguously confirms the [4 + 2] cycloaddition pathway (Figure 2) and

provides a general mechanistic picture for this allenic cycloaddition. Based on the NOE assignments of the respective major isomers for **16a** and **16b** (dr 3:1), the current mechanistic picture also implies that the furan approaches from the more hindered side with R ≠ H. We are not certain of reasons behind this contra-steric approach.

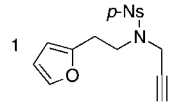
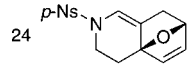
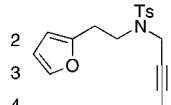
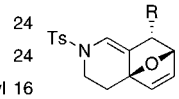
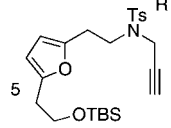
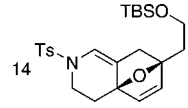
Second and more importantly, we recognized the possibility of developing a tandem sequence consisting of propargyl amide isomerization followed by cycloaddition. As shown in Scheme 2, in the presence of 20 mol % *t*-BuOK at 65 °C, isomerization of propargyl amide **8** and the ensuing cycloaddition led to **10** in 86% yield over three steps from furan (or two steps from commercially available 2-(furan-2-yl)ethanol **26**). Likewise, cycloadduct **29** could be obtained in 68% yield in two steps from furfuryl alcohol. We note here that without *t*-BuOK, this tandem process does not take place even after heating in toluene at 110 °C for 24 h, thereby suggesting that the tandem sequence proceeds through exclusively the respective allenamide intermediate.

In addition, with platinum or gold catalysts, the reaction proceeded through a very different pathway.[22,23] Moreover, in a related example from Kanemastu's account,[15] 5.0 equiv of *t*-BuOK was used and the reaction afforded ring-opened and aromatized products instead of furan-cycloadduct **29**. The use of catalytic amount of *t*-BuOK proves to be the key in accessing these structurally more useful cycloadducts.

Finally, this tandem process is general for a range of propargyl amides (Table 3) including those that are terminally substituted (entries 2−4), thereby also representing first examples of successful base-promoted isomerizations of terminally substituted propargyl amides to allenamides.[20,24] It is noteworthy that all propargyl amides employed here were prepared from respective furyl alcohols featuring a Mitsunobu reaction using *N*-sulfonylated propargyl amine (see **27** in Scheme 2), making this tandem process amenable for facile constructions of complex nitrogen heterocycles from very simple commercially available material.

We have described here a rare normal electron-demand [4 + 2] cycloaddition of *N*-tethered allenamides under thermal conditions without assistance of any metals. Our efforts also led to the development of an efficient and highly stereoselective tandem propargyl amide-isomerization−[4 + 2] cycloaddition sequence amenable for rapid assembly of highly functionalized nitrogen heterocycles from very simple commercial furyl alcohols. Applications of this method toward constructing isoquinoline-, quinoline-, or isoindole-containing natural products are underway.

Table 3. Tandem Isomerization−[4 + 2] Cycloadditions

entry	propargyl amides[a]	time [h]	cycloadducts	yield [%][b]
1	 **30**	24	 **14a**	84
2	 **31a:** R = Ph	24	 **16a**	79[c]
3	**31b:** R = Me	24		**16b**	42[c,e]
4	**31c:** R = *n*-pentyl	16		**16c**	25[d,e]
5	 **32**	14	 **19**	63

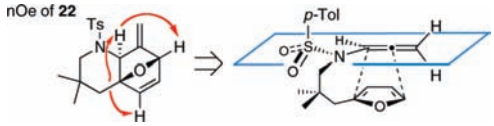
[a] Unless otherwise noted, all reactions were carried out in THF at concn = 0.10 M with 20 mol % of *t*-BuOK. For entries 1 and 5, reaction temp = 65 °C; for entries 3 and 4, temp = 85 °C; and for entry 2, temp = 25 °C. [b] Isolated yields. [c] dr = ∼3:1. [d] dr = ∼2:1. [e] The reaction was slower, and also observed was hydrolysis of the starting allenamide.

Acknowledgment. The authors are grateful for NIH-NIGMS funding (GM066055) and thank Dr. Vic Young, University of Minnesota for providing X-ray structural analysis.

Supporting Information Available: Experimental and ^{1}H NMR spectral and characterizations for all new compounds and X-ray structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

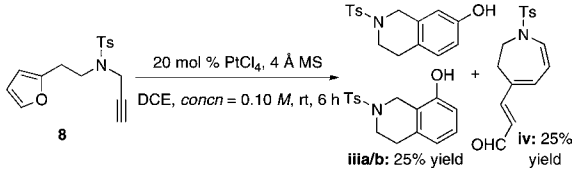
OL901283M

(21) NOE experiments of cycloadduct **22** and its possible cycloaddition transition state.



In addition, the regioisomeric cycloadduct **23** was found to equilibrate to **22** via retro-[4 + 2] and [4 + 2] after heating at 110 °C in toluene for 22 h.

(22) When using $PtCl_4$, we were able to isolate some products (**iii** and **iv**) that are related to those reported by Hashmi amd Echavarren (see ref 23).



(23) For leading references, see: (a) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Chem.—Eur. J.* **2006**, *12*, 6991. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. (c) Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4754.

(24) For a review, see: Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, 2005; Chapter 21.4.