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RECENT PROGRESS OF HALOGEN-DANCE REACTIONS IN HETEROCYCLES

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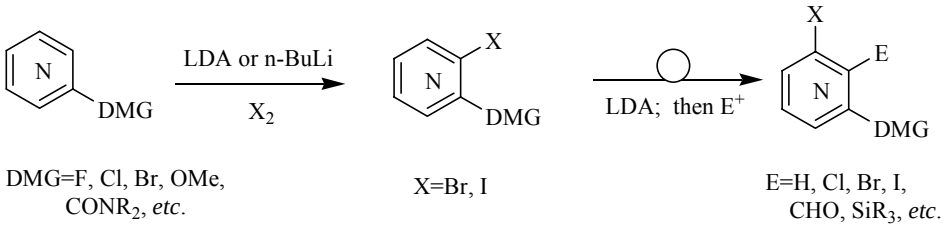
Abstract –This paper summarizes recent progress of halogen-dance reactions and its applications in heterocycles.

INTRODUCTION

Halogen-dance (HD) reactions, also referred to as halogen scrambling, halogen migration or based-catalyzed halogen dance (BCHD), [1] was first found by chance in 1953. [2] Since then researchers have been extensively studying this rearrangement. Their endeavors are reciprocated by following achievements: (1) significant extension of its scope; (2) illustration of its mechanism; (3) extensive applications in building novel or complicated compounds. These have been summarized in three reviews[3-5] among which the most recent review was published in 1996. This review gives a summury of halogen dance reactions after 1996. We focus on the migrations in heterocycles [6,7] including pyridines, quinolines, thiazoles and pyrazoles.

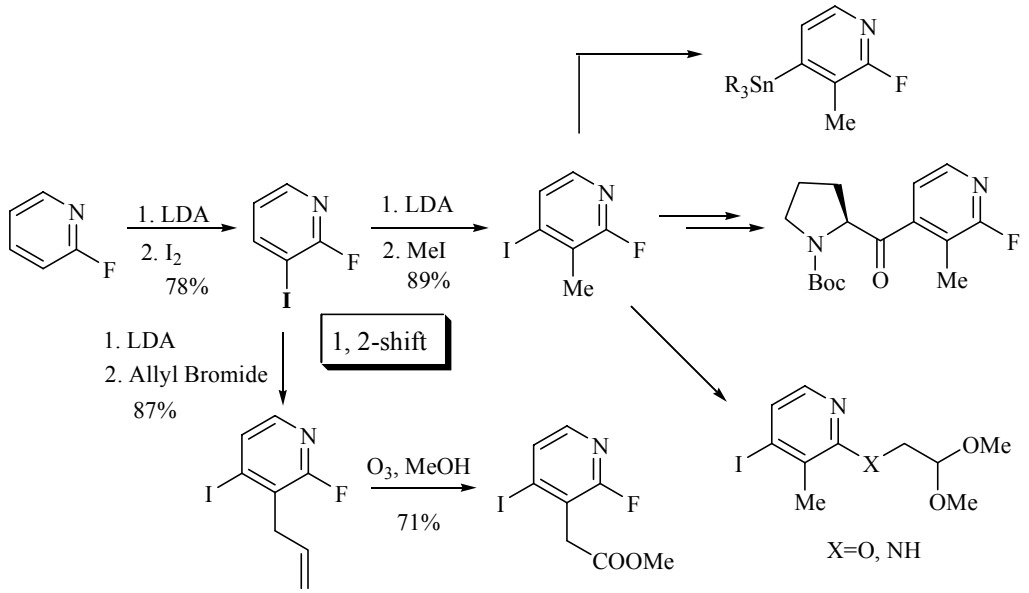
Halogen Dance Reactions in Pyridines

Halogen migrations in pyridines were first proposed by den Hertog during the amination of 3-bromo-4-ethoxypyridine [8] in 1962 and investigated in detail later by Quéguiner. [9] The results listed in Table (Entries Py01~11) summarize the recent findings of the halogen dance reactions of pyridine halorides.



Scheme 1

The typical pattern of the halogen dances of pyridine compounds can be demonstrated as in Scheme 1. The rearrangement usually takes place as 1,2-halogen shift. This furnishes us with a new and convenient synthetic approach to 1,3–disubstitued and 1,2,3-trisubstituted pyridines (Entries Py01~07). Saitton (Entry Py02) gave an excellent demonstration in exploiting the migrations (Scheme 2). [12, 13]

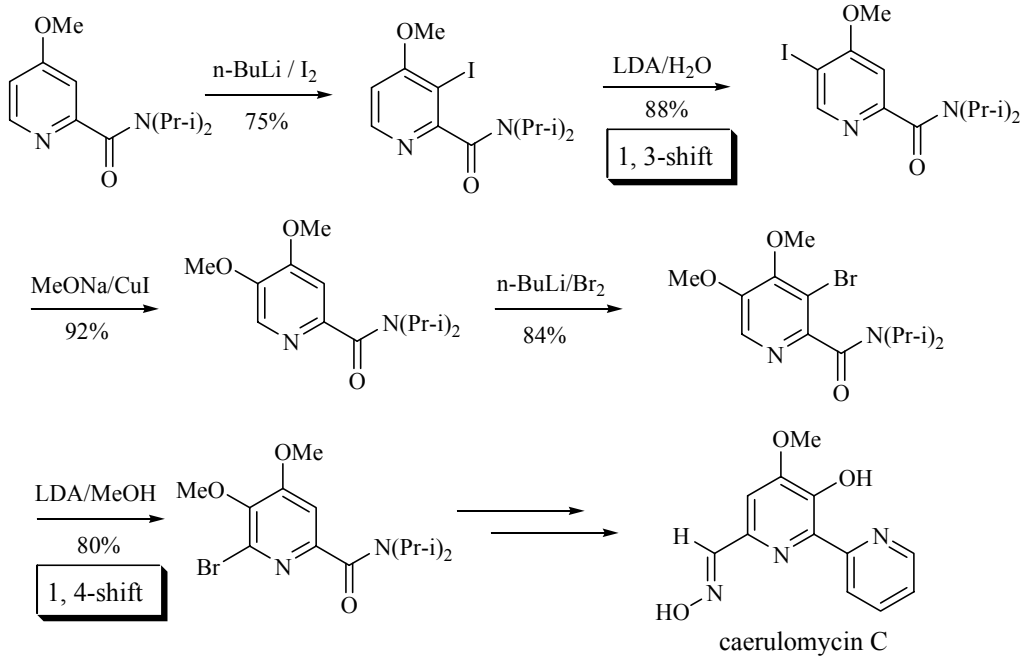


Scheme 2

The variety of DMG (as denoted in Scheme 1) remarkably widens the scope of this synthetic approch. Among halogens fluorine and chlorine atoms are familiar DMGs because they hardly migrate.[5] On the contrary bromine and iodine atoms seldom serve as DMGs for their lability of shift.[5,10,11] In 2004, we provided an example in which bromine atom acted as DMG and 2-bromo-4-iodopyridine was efficiently synthesized *via* halogen dance (Entry Py06).[16]

In addition to 1,2-halogen shifts, 1,3-halogen–shifts (Entries Py09~11) and 1,4-shifts (Entry Py09) can also be conducted. By means of 1,3-halogen-shifts, Schlosser and collaborators (Entry Py10) prepared a series of multi-substituted pyridine derivatives.[15, 22]

In the total synthesis of caerulomycin C (also prepared by Quéguiner *et al. via* 1,2-halogen dance as in Entry Py08), Sammakia utilized 1,3, 1,4 – halogen dance reactions as key steps to incorporate two functional groups (Scheme 3).[21] Obviously the diversity of halogen dance reactions allows the flexible functionalization of heterocycles in ways that would be difficult or impossible through classical means.



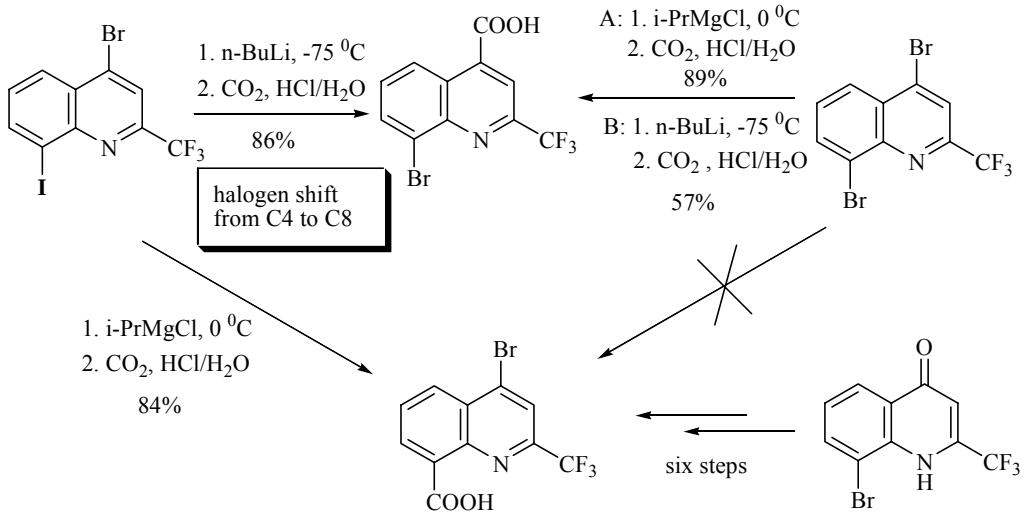
Scheme 3

Halogen Dance Reactions in Quinolines, Thiazoles and Pyrazoles

Halogen dance reactions of quinolines halides were first carried out by Quéguiner *et al*. in 1998. Treatment of 4-iodo-3-fluoroquinoline with LDA followed by electrophiles led to 1,3- iodine shifted products.[24] Taking advantage of the rearrangement Quéguiner *et al*. performed syntheses of quindoline, cyptomisrine as well as benzo-δ-carbolines, cryptolepines and their salts (Entries Qu01~02).[25, 26]

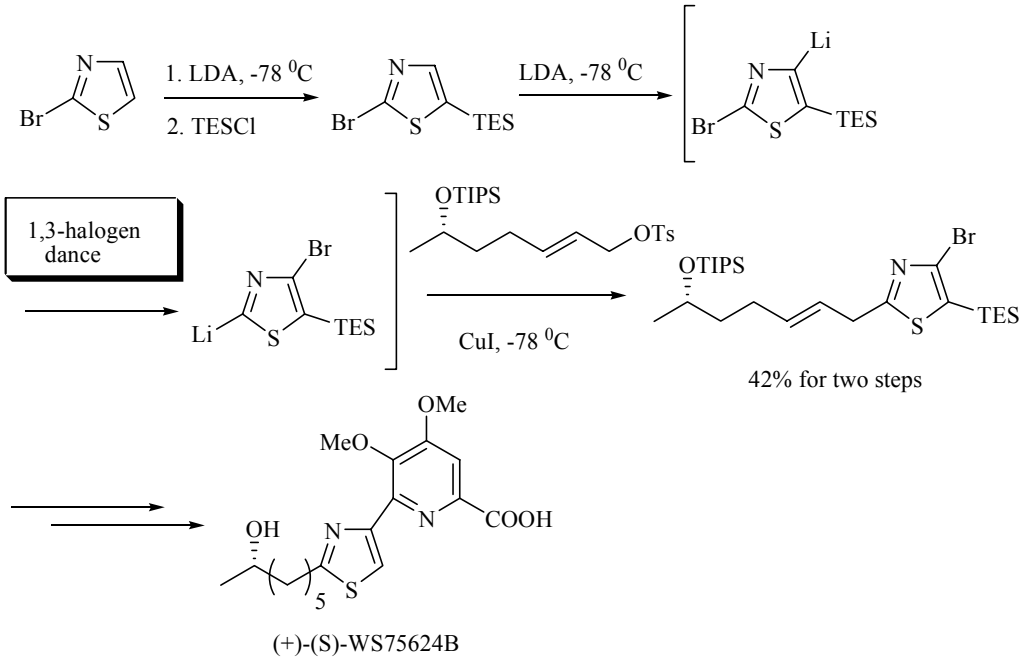
In contrast to the iodine's migration in pyridine nucleus of quinolines, Blakemore practiced 1,3-iodine shifts in benzene ring during their synthesis of 6,6'-disubstituted 7,7'-dihydroxy-8,8'-biquinolyls (Entry Qu03).[27]

It is interesting that a halogen dance across pyridine and benzene nucleus of quinoline (from C8 to C4) was also reported (Entry Qu04).[28] Schlosser proposed this migration on the basis of alternate metalations of different substrates (Scheme 4).[28]



Scheme 4

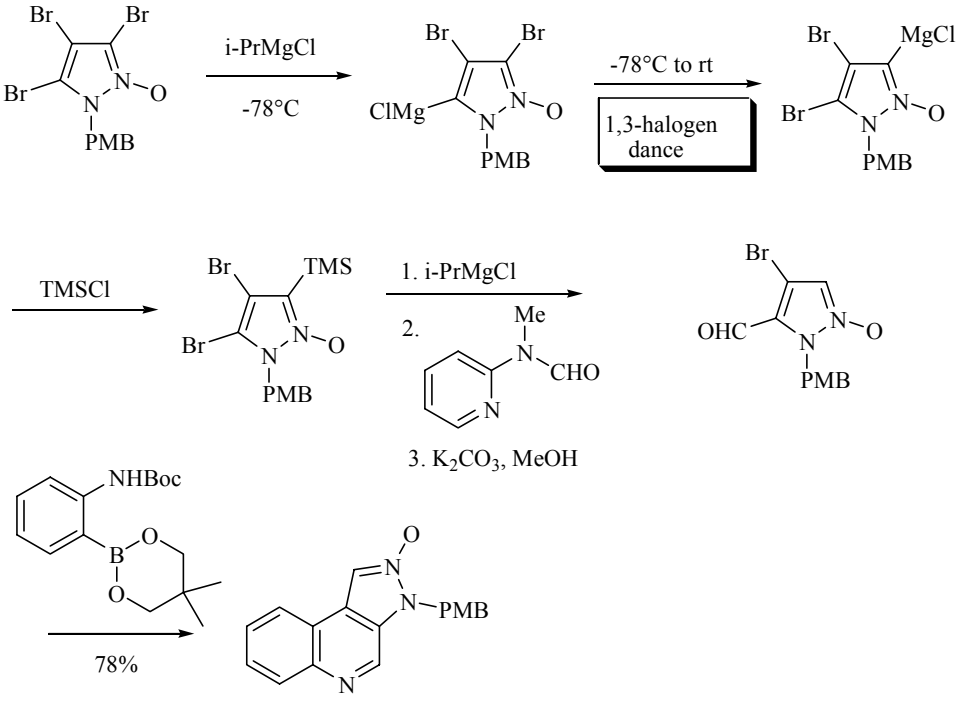
During the total synthesis of WS75624 B, Stangeland practiced various halogen dance of thiazoles (Entry Tz).[29] The rearrangement enabled them to build 2,5-disubstituted thiazoles facilely which are rather difficult to obtain through classical means (Scheme 5).[29]



(+)-(S)-WS75624B

Scheme 5

Halogen dance reactions of aromatic halorides have been induced mostly by LDA or n-BuLi through deprotonation or lithium-halogen exchange although they were promoted early by Na or K amides. [5] In 2002, Eskildsen reported an unprecedented 1,3-halogen dance reaction of pyrazole 1-oxides in which the migration was initiated by bromine-magnesium exchange (Entry Pzo).[30] The authors found that raising the reaction temperature from –78 °C to room temperature promoted the migration to completion. This rearrangement provided access to 3,4-disubstituted pyrazoles which were utilized to synthesize a series of pyrazolo[3,4-*c*]quinoline 1-oxides (Scheme 6).[30]

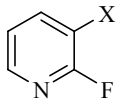
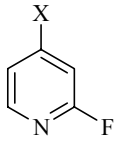
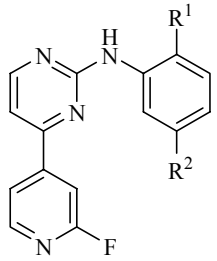
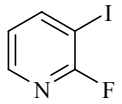
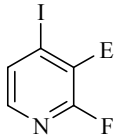
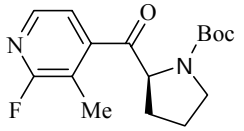
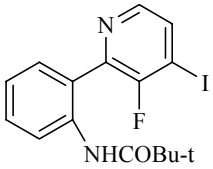
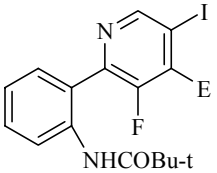
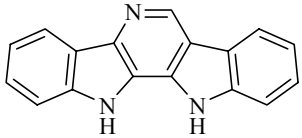
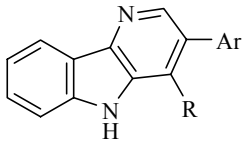
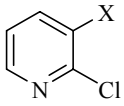
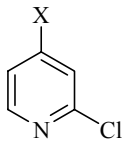
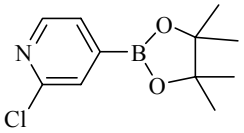
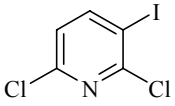
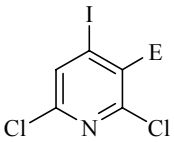
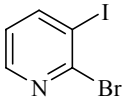
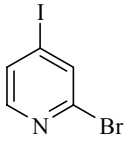
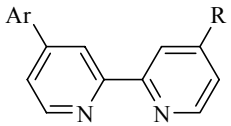
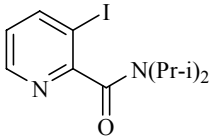
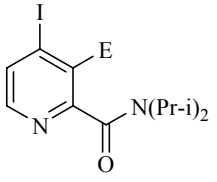
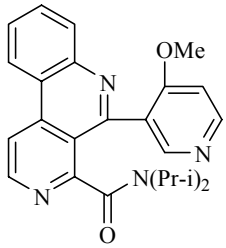


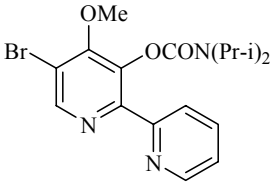
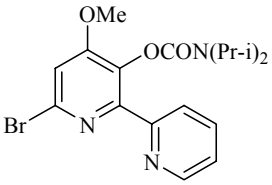
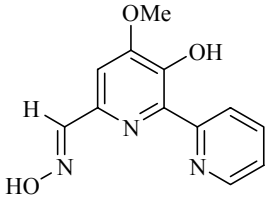
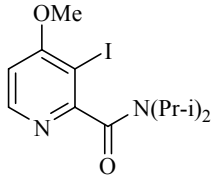
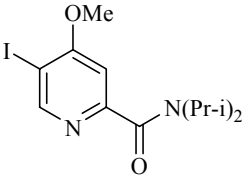
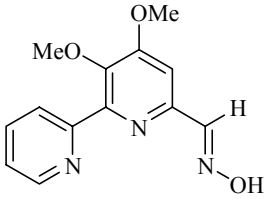
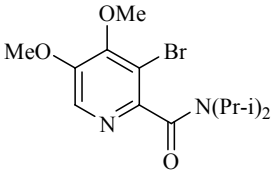
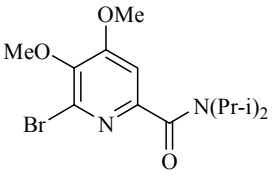
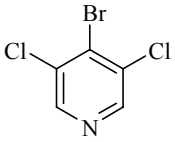
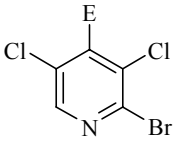
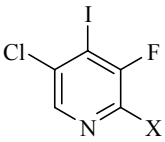
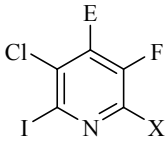
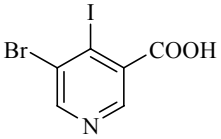
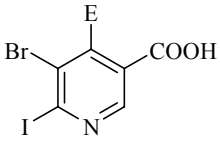
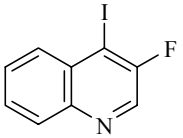
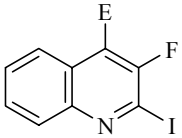
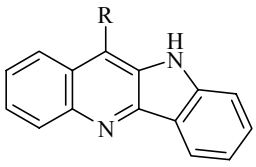
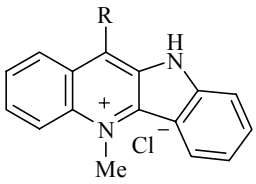
Scheme 6

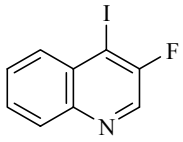
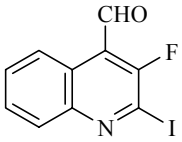
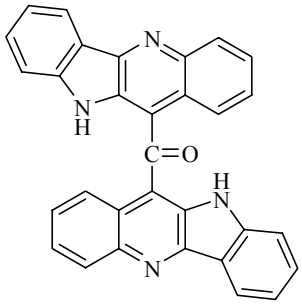
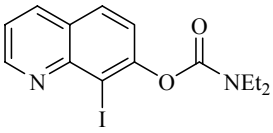
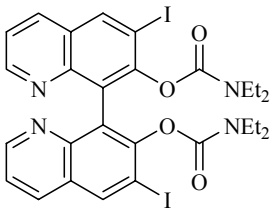
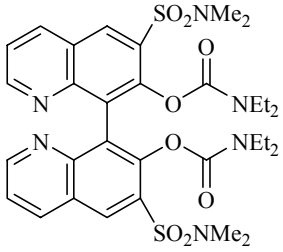
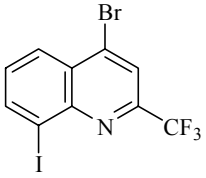
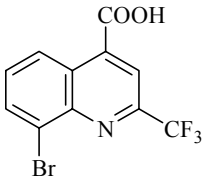
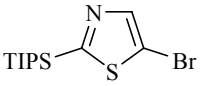
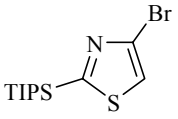
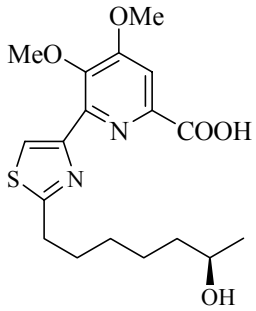
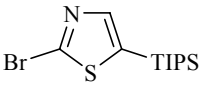
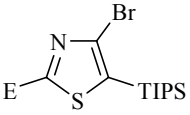
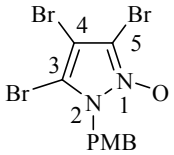
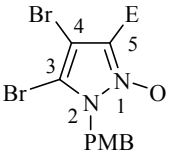
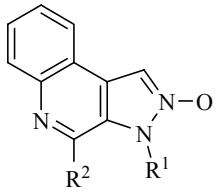
CONCLUSION REMARKS

Halogen dance reactions were first discovered by chance and, to some extent, regarded as side-reactions to prevent. Since the first example of controlled halogen dance at a thiophene derivative was reported by Kano, [31] this rearrangement has turned out to be a useful synthetic tool to many novel compounds. In the classical metalation of halorides, the functional groups are fixed to (*via* metal-halogen exchange) or ortho to (*via* deprotonation) the positions of halogen atoms. Halogen dance reactions enable us to introduce functional groups at other positions to halogens. This really makes halogens a great helper in organic synthesis.

Table Halogen-Dance Reactions and Applications in Heterocycles

Entry	Substrates	Reagents (Yield)	Products of Halogen-Dance	Derivatives of H- D Products	Ref.
Py01		1. LDA/THF 2. H_2O X = I (98%); Br (-)		 R^1 = H, Halogen, Alkyl, *etc.* R^2 = H, Alkyl, Alkoxy, *etc.*	10, 11
Py02		1. LDA/THF 2. H_2O, *etc.* (13∼89%) E = H, Me, Bn, Allyl, *etc.*			12, 13
Py03		1. LDA/THF 2. H_2O, *etc.* E= H (91%); I (80%); Cl (82%), CHO (80%); *etc.*		  Ar = Ph, 2-NH_2Ph, 2-Pyridyl, 2-Thienyl, *etc.* R = H, Me, Ph	14
Py04		1. LDA/THF 2. H_2O X = I (79%); Br (-)			11, 15
Py05		1. LDA/THF 2. H_2O, *etc.* E = H (68%); COOH (57%)			15
Py06		1. LDA/ ether or THF 2. H_2O Ether (86%); THF (80%)		 Ar = 4-MePh R = 4-MePh , H	16, 17
Py07		1. LDA/THF 2. H_2O, *etc.* E= H(78%); I (87%); CHO (82%); *etc.*			18, 19

Py08		1. LDA/THF 2. H_2O (85%)		 caerulomycin C	20
Py09		1. LDA/THF 2. H_2O (88%)		 caerulomycin C	21
		1. LDA/THF 2. H_2O (80%)			
Py10		1. LDA/THF 2. H_2O, *etc*. E = H (42%); COOH (41%)			15 22
	 X= Cl; Br; I	1. LTMP or LDA /THF 2. H_2O, *etc*. E = H (23~46%); COOH (82~89%)			
Py11		1. LDA/THF 2. H_2O, *etc*. E = H (45%); D (47%)			23
Qu01		1. LDA/THF 2. H_2O, *etc*. E = H (95%); I (98%); Cl (74%); Me (65%); etc.		  R = H, Me, Et, Pr-i, Ph	24, 25

Qu02		1. LDA/THF 2. HCOOEt/THF 3. H_2O (95%)			26
Qu03		1. LDA/THF 2. $FeCl_3$ (54%)			27
Qu04		1. n-BuLi/THF 2. CO_2 (57%)			28
Tz		LDA/THF; then H_2O (86%)			29
		LDA; then H_2O, *etc*. E = H (85%); CH_3 (82%); etc.		(+)-(S)-WS75624 B	
Pzo		1.i-PrMgCl/THF, -78°C 2. -78°C to rt; 3. H_2O, *etc*. E = H(88%); TMS(100%)		 R^1 = PMB, Bn R^2 = H, Me, Et, Ph	30

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