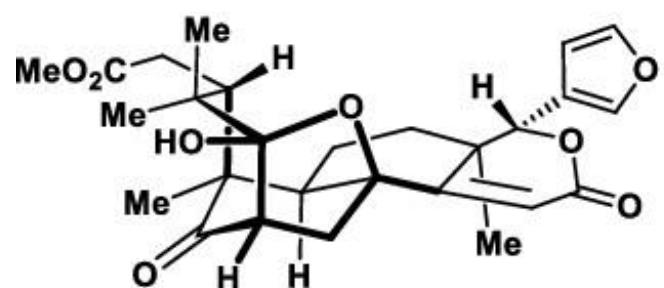
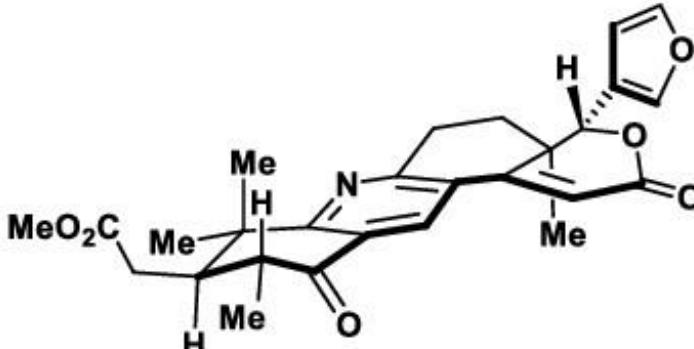


Total Synthesis of (+)-Haperforin G

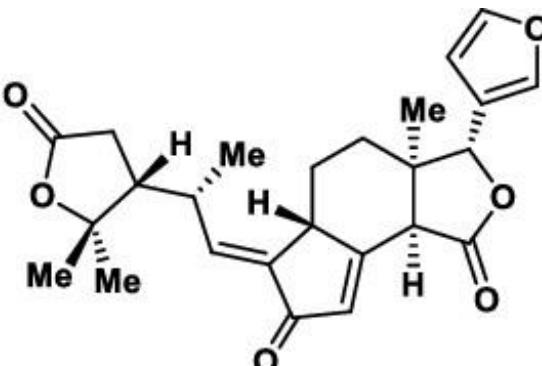
Wei Zhang, Zhenyu Zhang, Jun-Chen Tang, Jin-Teng Che, Hao-Yu Zhang, Jia-Hua Chen,*
and Zhen Yang*



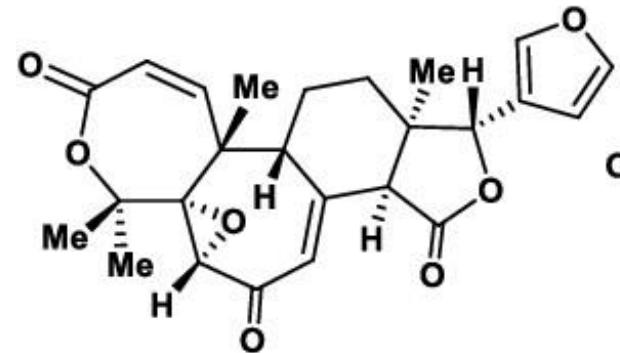
andirolide N (1)



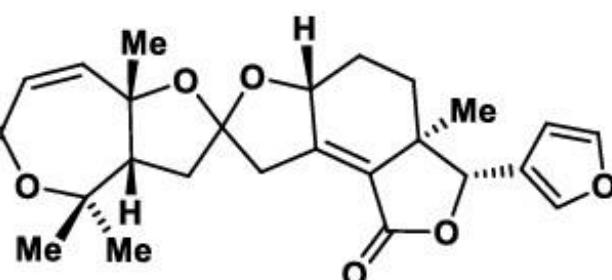
xylogranatopyridine B (2)



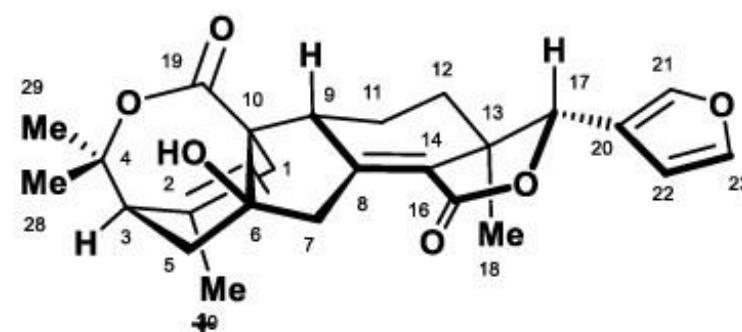
perforanoid A (3)



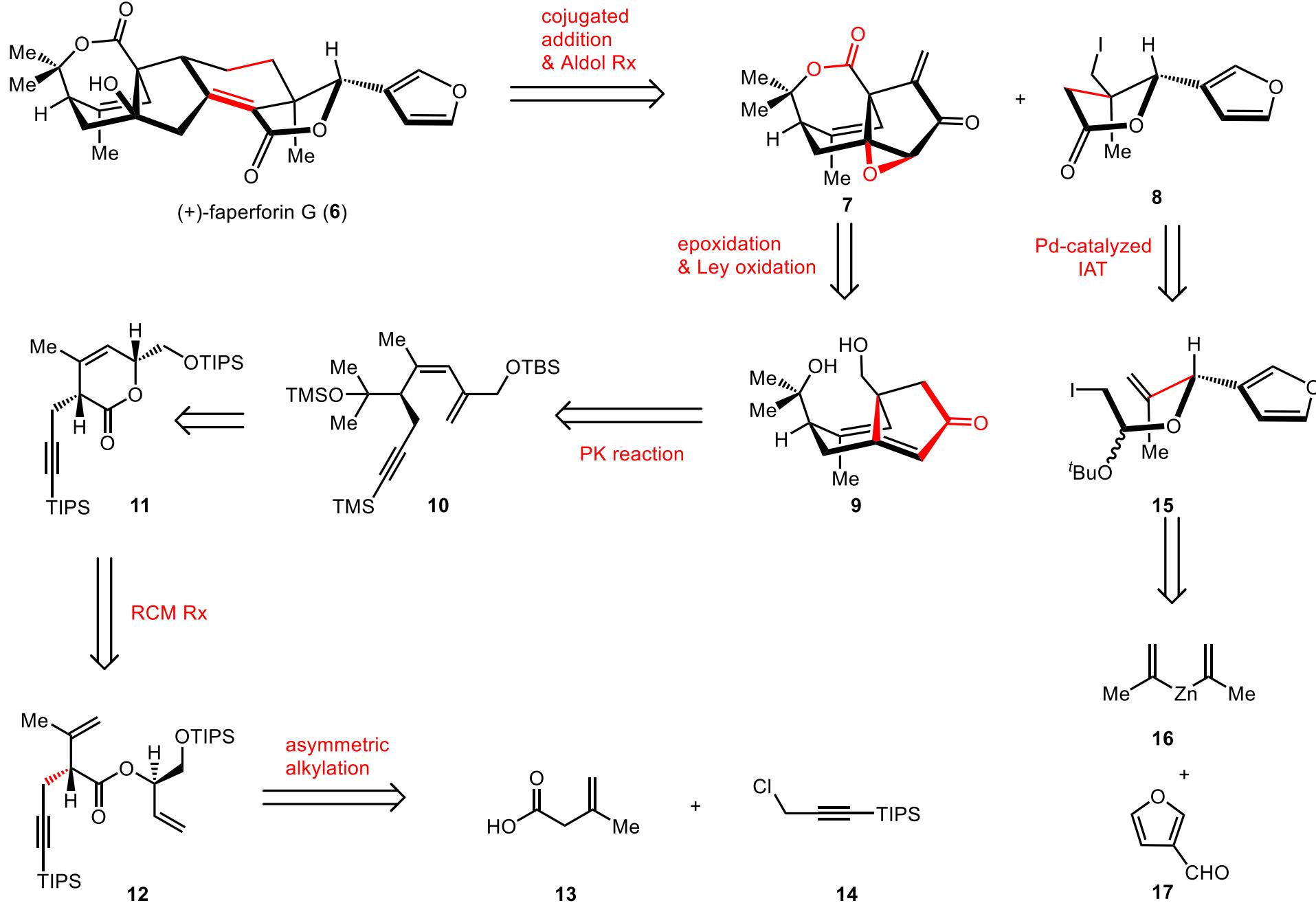
haperforin C2 (4)

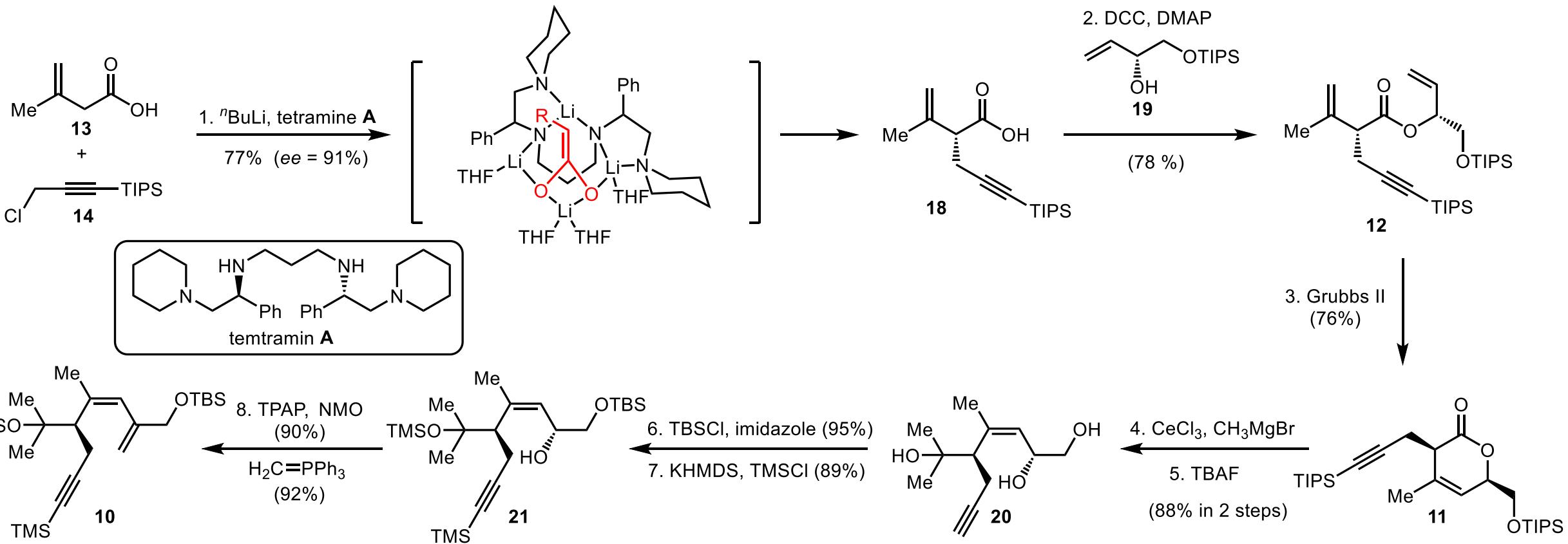


harperspinoids A (5)

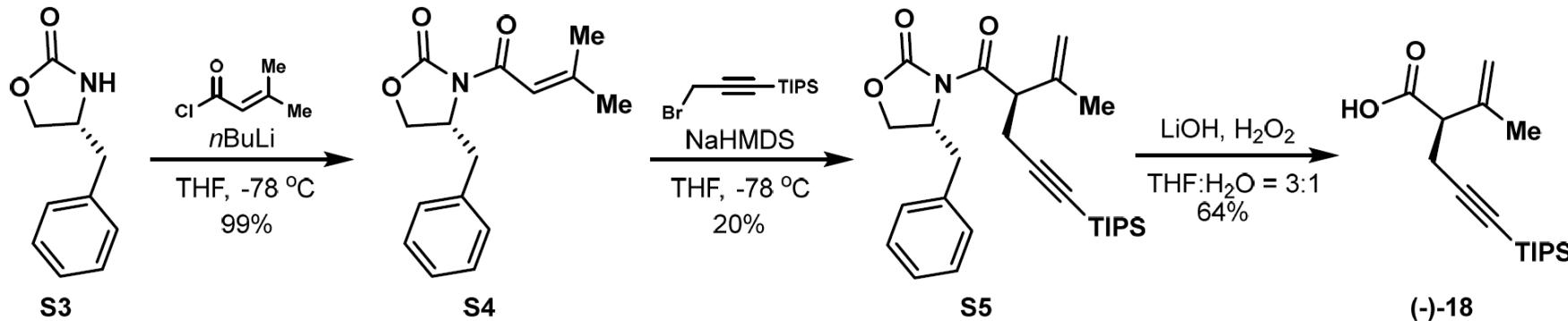


haperforin G (6)

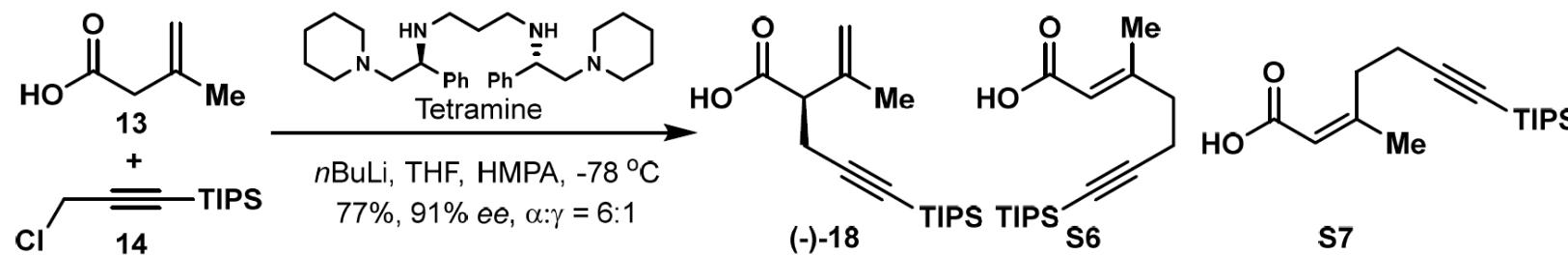




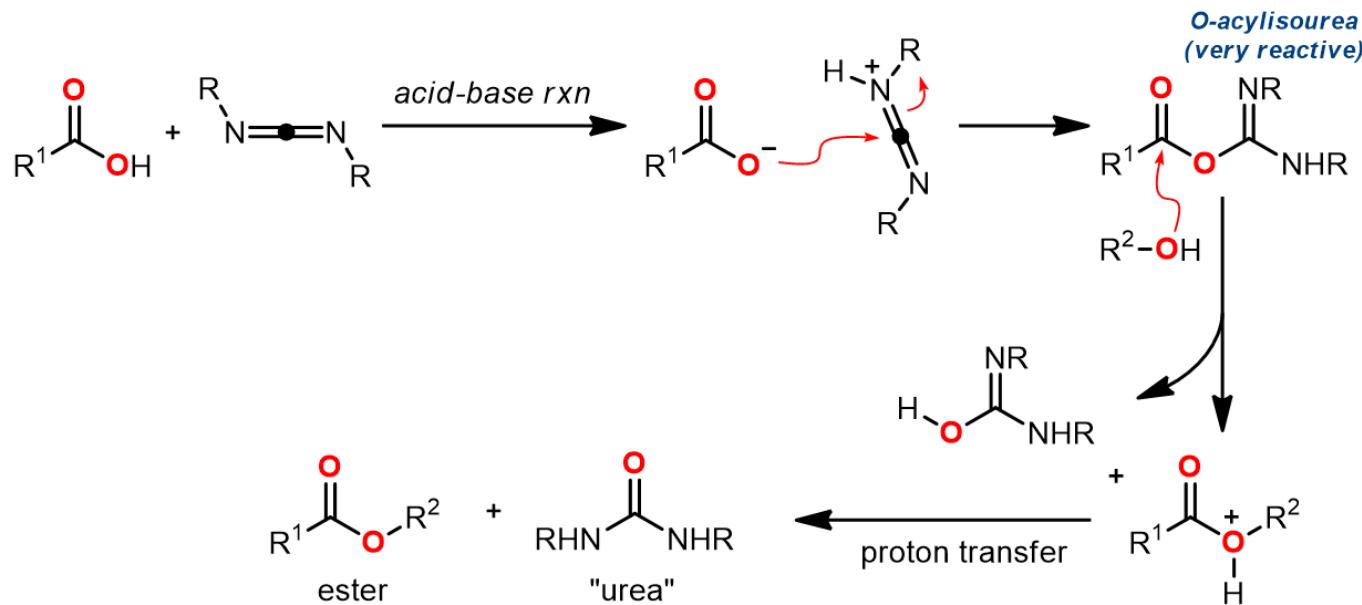
Synthesis of compound (-)-18 (Method A)



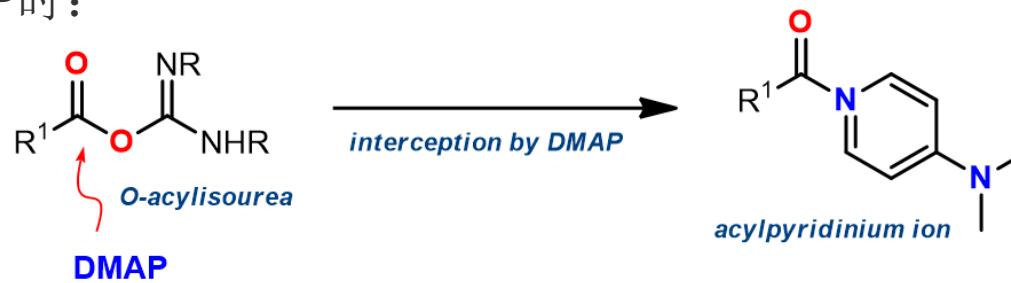
Synthesis of compound (-)-18 (Method B):



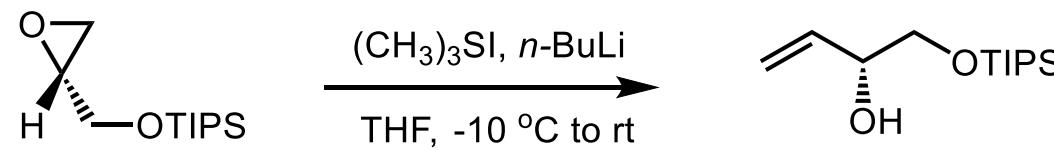
Steglich酯化反应



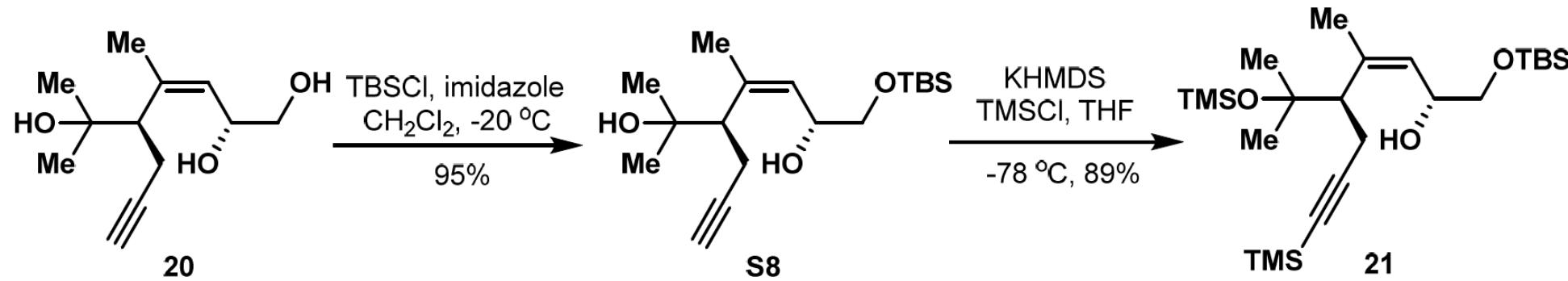
当反应体系中加入催化量的DMAP时：



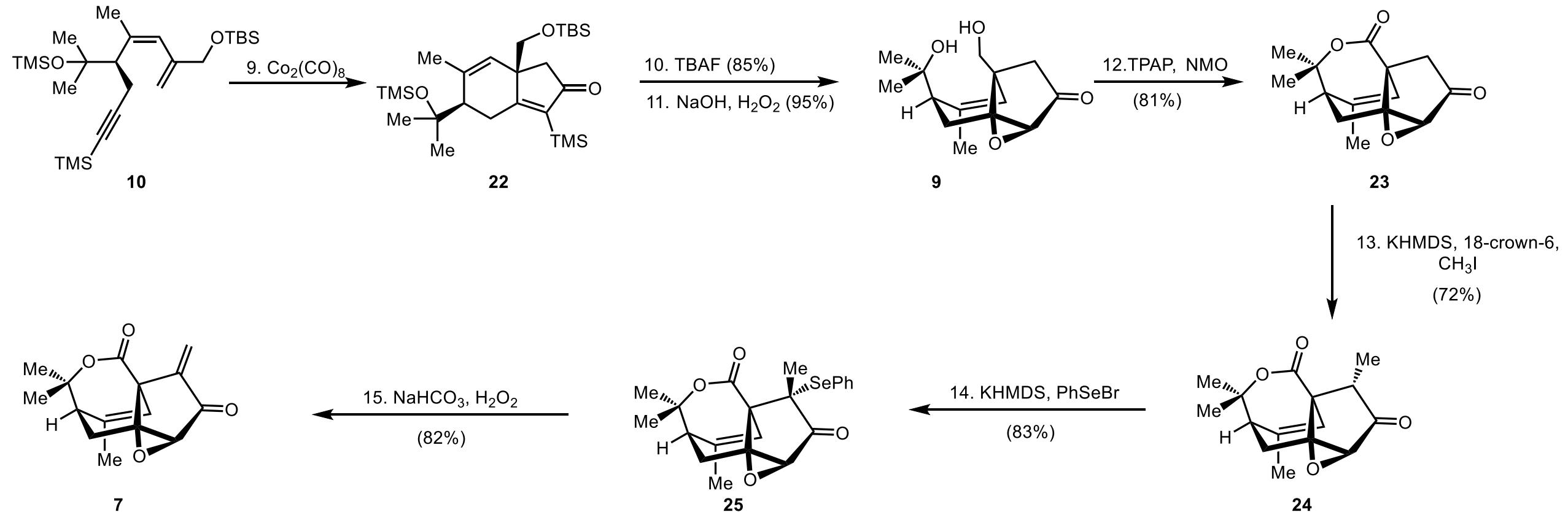
化合物**19**的合成：



Synthesis of compound 21



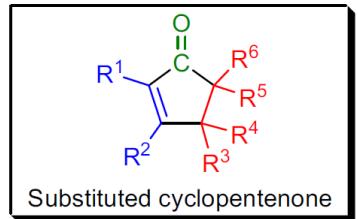
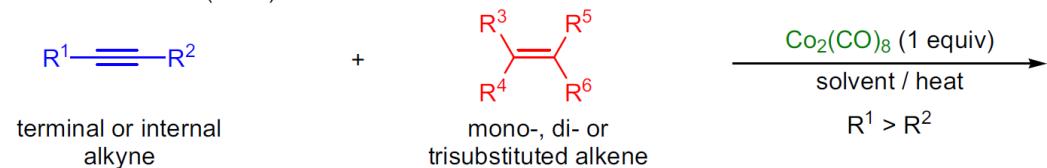
To a stirred solution of **S8** (7.10 g, 21.78 mmol) and TMSCl (18.93 g, 174.24 mmol) in THF (220 mL) at 0°C was added KHMDS (130.7 mL, 1.0 M in THF , 130.70 mmol) over 1 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (500 mL) and the mixture was extracted with EtOAc (800 mL), the organic layer was washed with HCl (500 mL, 0.5 M in water) and brine (2 x 500 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether : EtOAc = 100:1 to 50:1) to give **21** (9.11 g, 89%) as colorless oil.



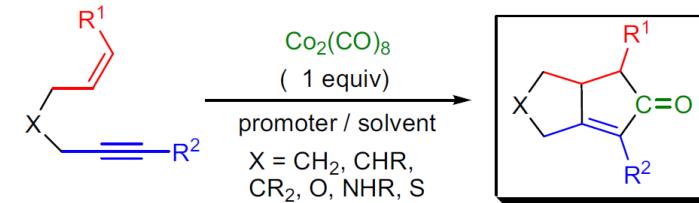
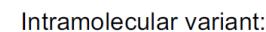
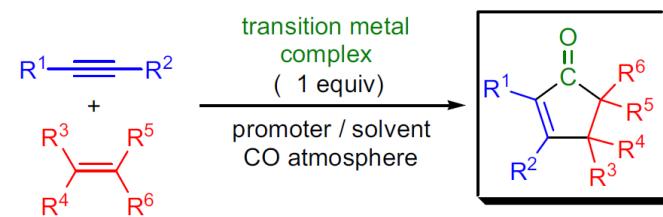
PAUSON-KHAND REACTION

(References are on page 647)

Pauson & Khand (1973):



Modified P-K reaction:



R^{1-6} = H, alkyl, aryl, substituted alkyl and aryl; **transition metal complex**: $Co_2(CO)_8$, $Fe(CO)_5$, $Ru_2(CO)_{12}$, Cp_2TiR_2 , $Ni(COD)_2$, $W(CO)_6$, $Mo(CO)_6$, $[RhCl(CO)_2]_2$; promoter: NMO, TMAO, $RSCH_3$, high-intensity light/photolysis, "hard" Lewis base

Mechanism:

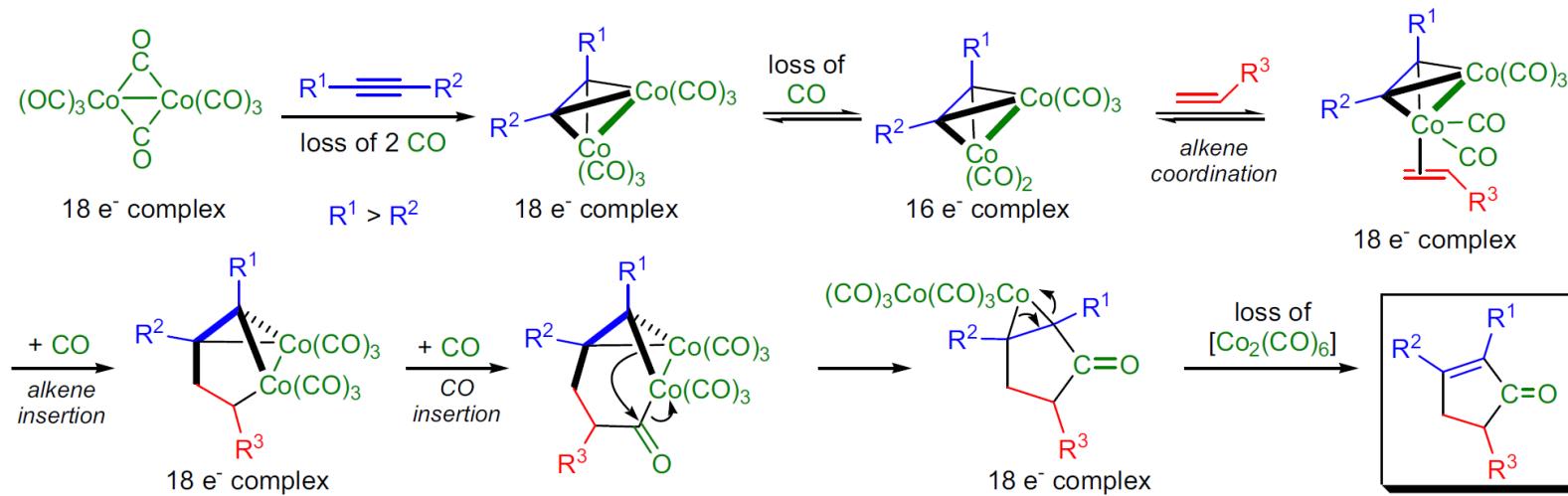
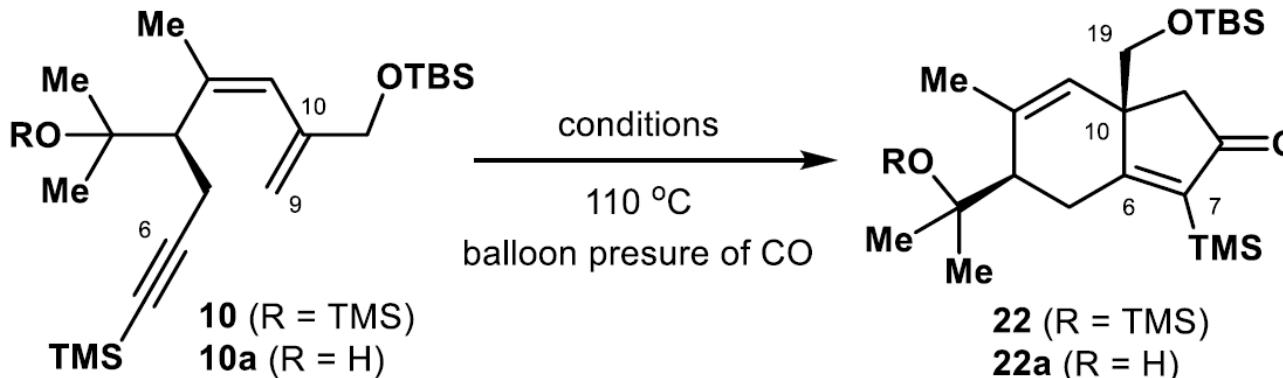
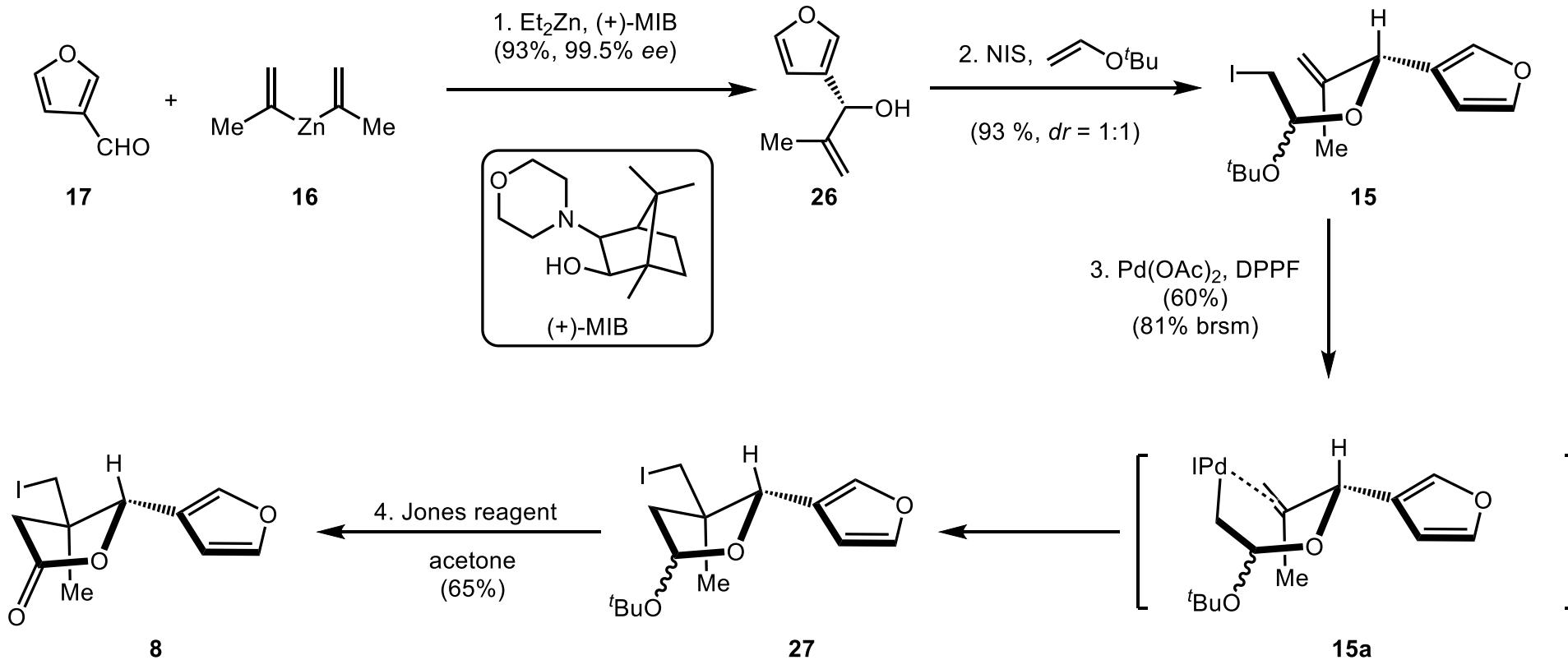


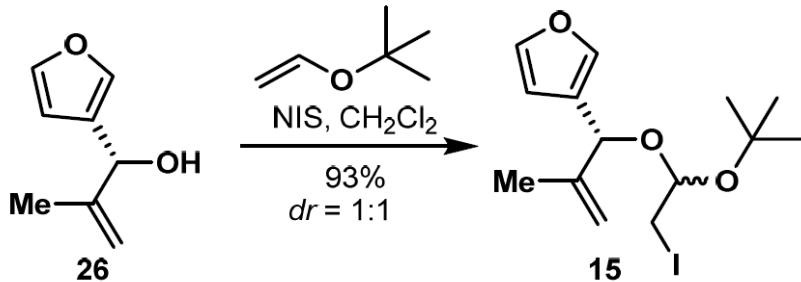
Table 1. Evaluation of Co-Mediated Reaction Conditions



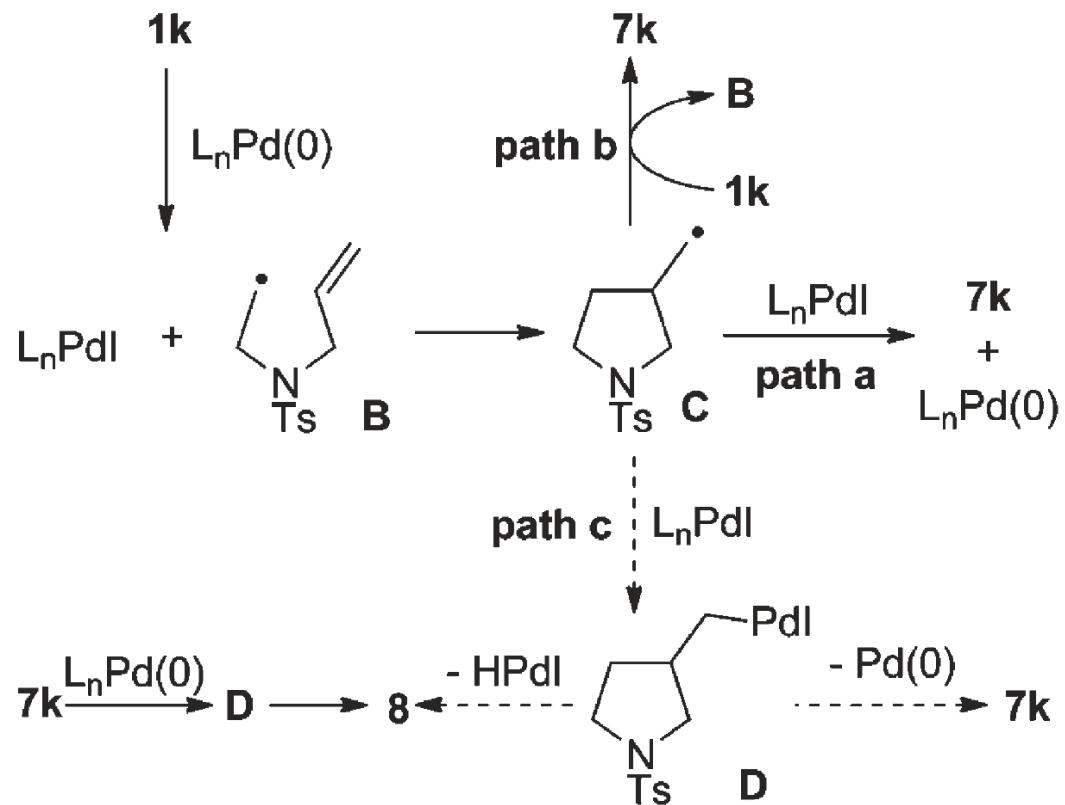
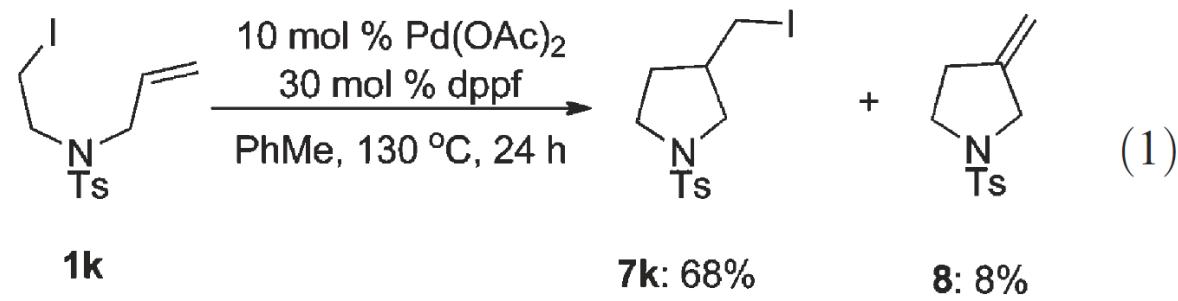
| entry | conditions | results |
|-------|---|---|
| 1 | 10a (1 equiv), $\text{Co}_2(\text{CO})_8$ (1.2 equiv), Et_2O , 1.5 h; then toluene, 24 h ^a | dr > 20:1; ^c 40% ^d |
| 2 | 10a (1.0 equiv), $\text{Co}_2(\text{CO})_8$ (1.2 equiv), toluene, 24 h ^a | dr > 20:1; ^c 40% ^d |
| 3 | 10a (1.0 equiv), $\text{Co}_2(\text{CO})_8$ (0.8 equiv), toluene, 24 h ^a | dr > 20:1; ^c 52% ^d |
| 4 | 10a (1.0 equiv), $\text{Co}_2(\text{CO})_8$ (0.8 equiv), toluene, 24 h ^b | dr > 20:1; ^c 57% ^d |
| 5 | 10a (1.0 equiv), $\text{Co}_2(\text{CO})_8$ (0.2 equiv), toluene, 36 h ^b | dr > 20:1; ^c 85% ^d |
| 6 | 10 (1.0 equiv), $\text{Co}_2(\text{CO})_8$ (0.2 equiv), toluene, 36 h ^b | dr > 20:1; ^c 86% ^d |

^aReactions concentration conducted on 0.1 M. ^bReactions concentration conducted on 0.01 M. ^cDetermined by ^1H NMR spectroscopy.
^dIsolated yield after purification by silica gel chromatography

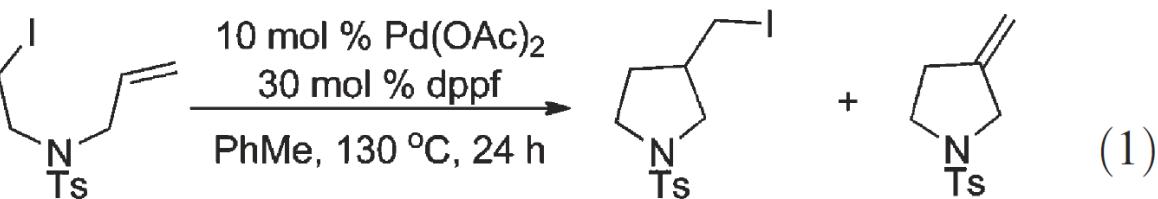




To a solution of **26** (1.63 g, 11.80 mmol) in CH_2Cl_2 (24 mL) was added *t*-butyl vinyl ether (1.42 g, 14.20 mmol). To this mixture was added NIS (3.19 g, 14.20 mmol) at -30 °C in portion-wise manner, and the resultant mixture was stirred at the same temperature for 20 min. The reaction mixture was quenched by slowly addition of a saturated solution of NH_4Cl (50 mL), and the mixture was extracted with EtOAc (2 x 100 mL). The combined organic layer was sequentially washed by $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) and brine (2 × 50 mL), and dried over anhydrous Na_2SO_4 . The solvent of the extract was concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (petroleum ether : EtOAc = 100:1) to give product **15** (4.02 g, 93%, *dr* = 1:1) as a mixture of diastereoisomers.



Scheme 3 Proposed mechanism.



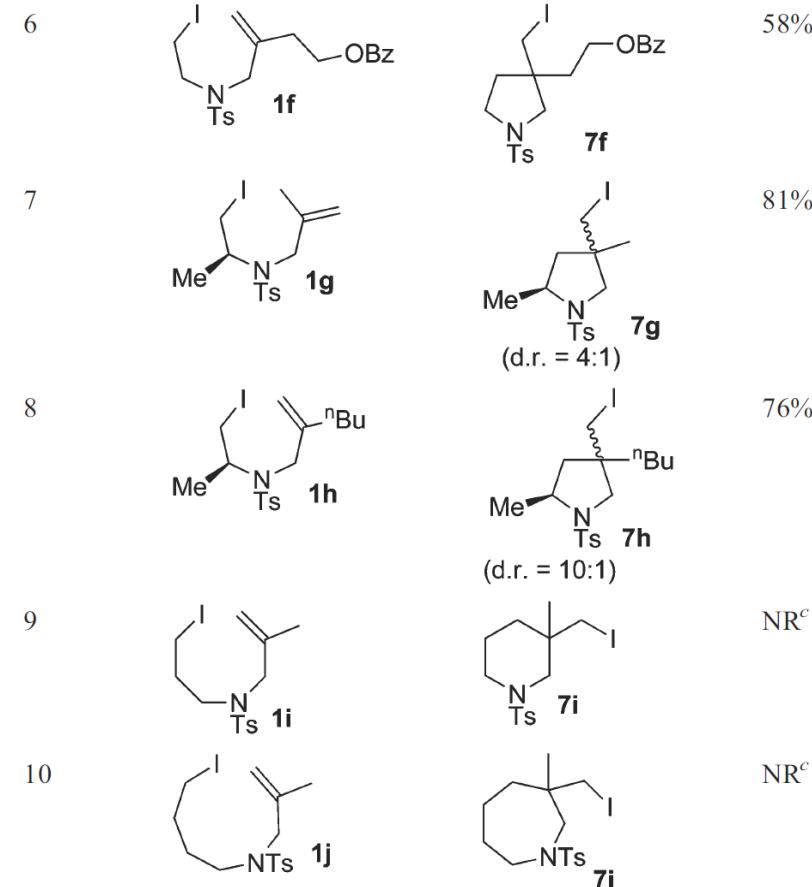
1k

7k: 68%

8: 8%

Table 2 Pd(0)-catalyzed IATC^a

| Entry | Substrate | Product | Yield ^b |
|-------|-----------|---------|--------------------|
| 1 | | | 82% |
| 2 | | | 70% |
| 3 | | | 68% |
| 4 | | | 35% |
| 5 | | | 72% |



^a Reactions run 0.05 M in PhMe at 130 °C with the use of Pd(OAc)₂ (0.02 mmol, 4.6 mg) and dppf (0.06 mmol, 34 mg) for 24 h. ^b Isolated yield. ^c No reaction.

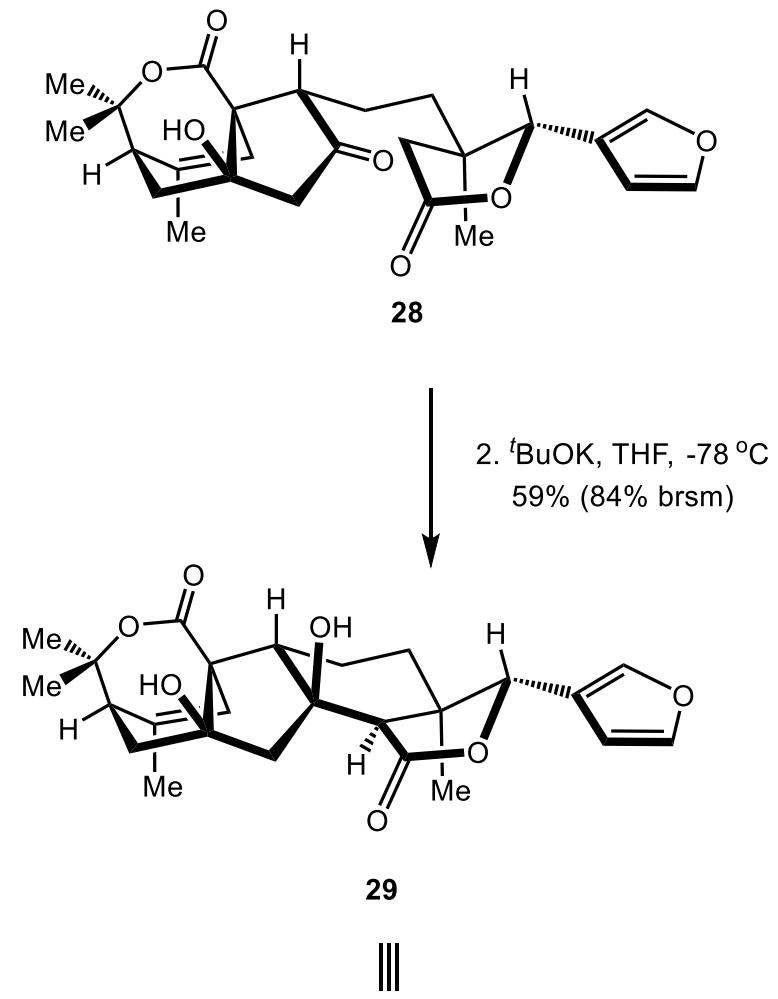
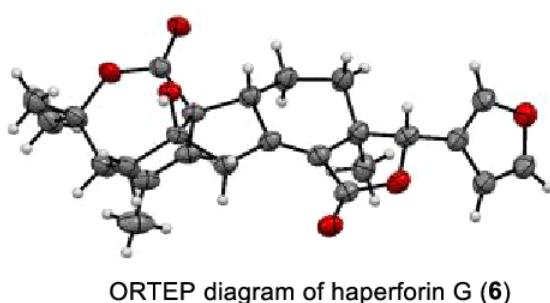
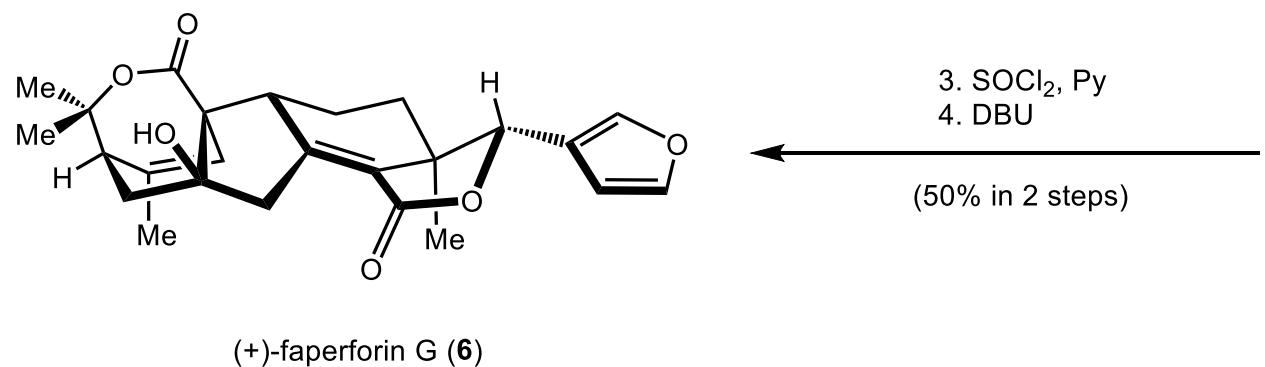
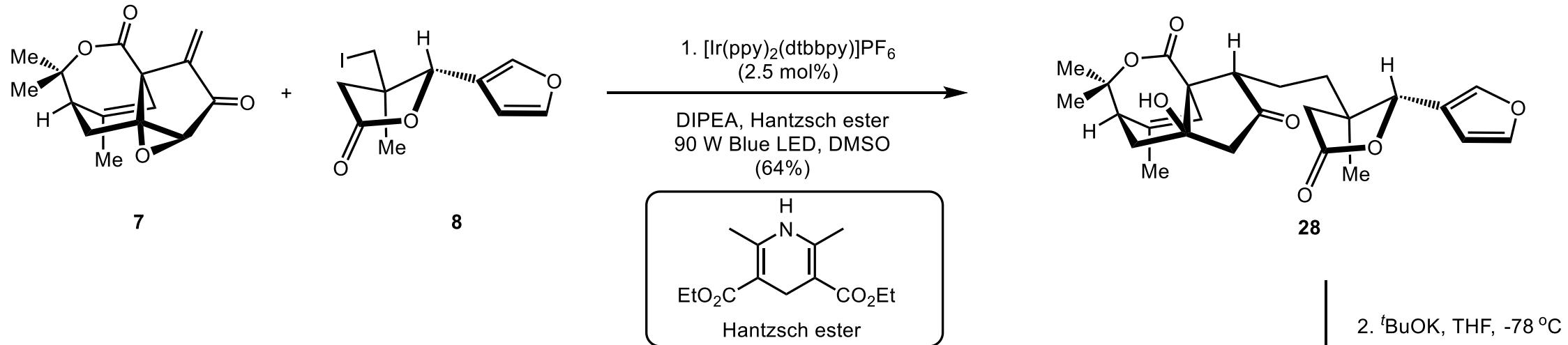
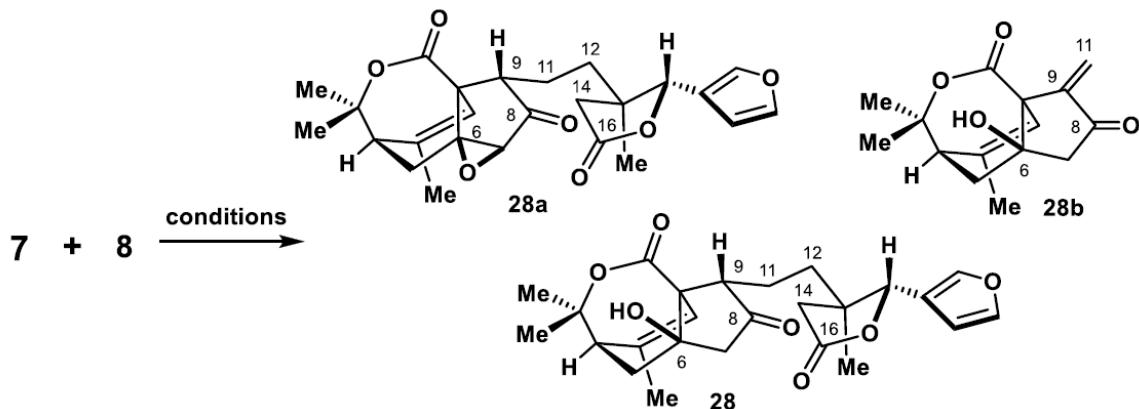
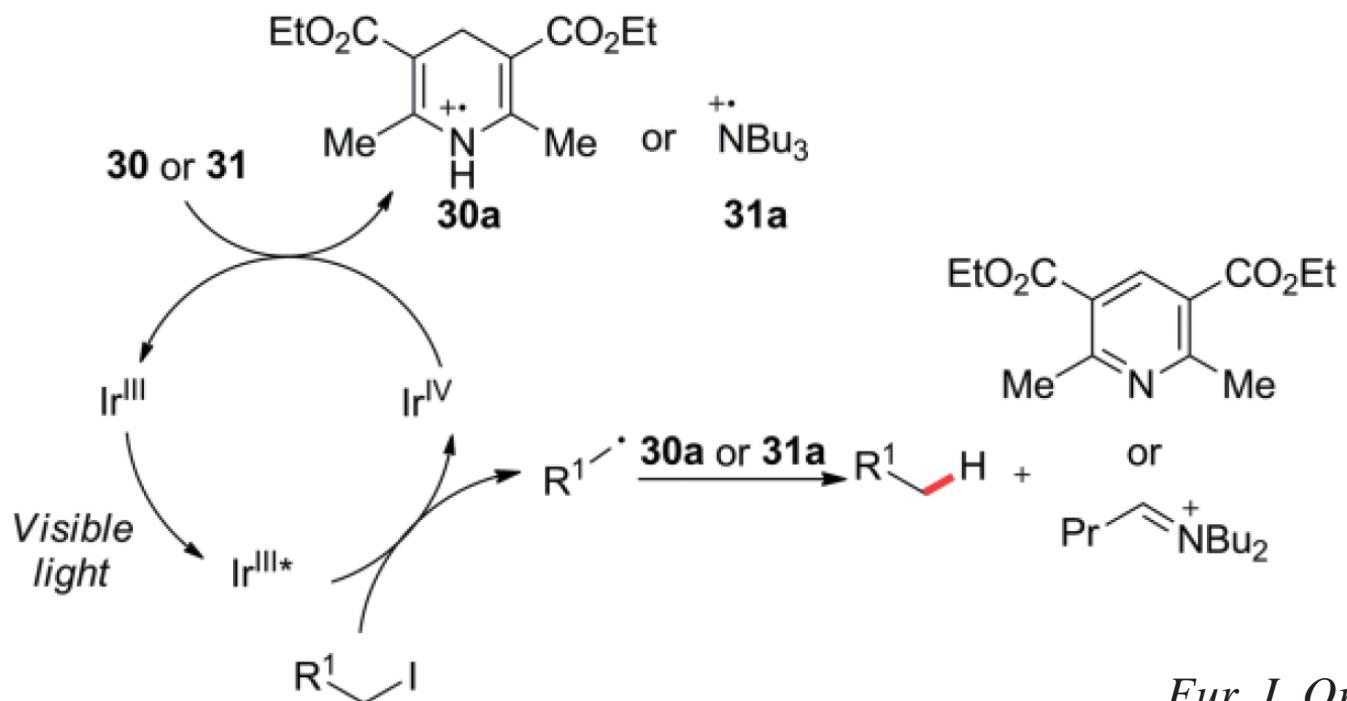
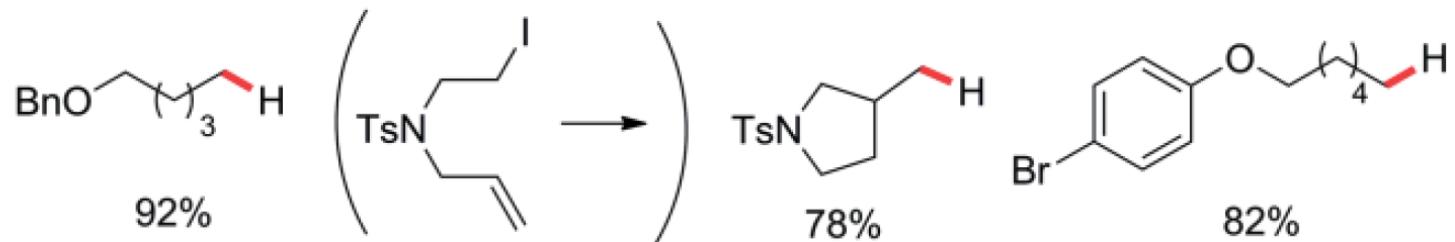
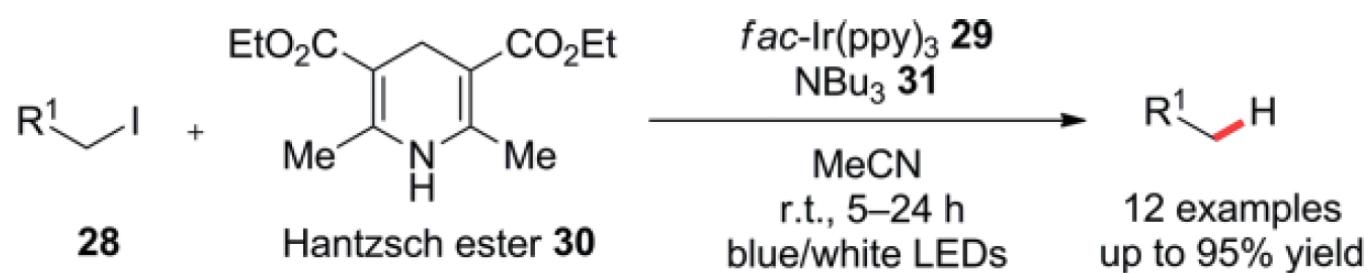


Table 2. Evaluation of Alkyl Radical-Based Coupling Reaction of Iodide 8 with Enone 7

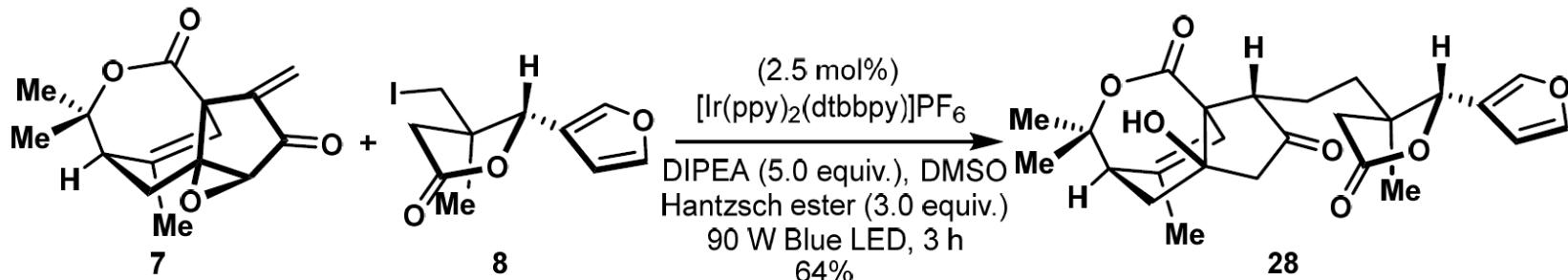


| entry | conditions ^a | results ^b |
|-------|--|-----------------------------|
| 1 | AIBN, Bu ₃ SnH, benzene, 2 h, 80 °C | dr > 20:1; 21% ^c |
| 2 | AIBN, Bu ₃ SnH (syringe pump), benzene, 2 h, 80 °C | dr > 20:1; 40% ^c |
| 3 | fac-Ir(ppy) ³ (2.5 mol %), DIPEA (2.0 equiv), MeCN 90 W Blue LED, 12 h, rt | dr > 20:1; 30% ^d |
| 4 | [Ir(ppy) ₂ (dtbbpy)]PF ₆ (2.5 mol %), Et ₃ N (2.0 equiv) DMF, 90 W Blue LED, 20 min, rt | dr > 20:1; 45% ^d |
| 5 | [Ir(ppy) ₂ (dtbbpy)]PF ₆ (2.5 mol %), DIPEA (2.0 equiv), MeCN, 90 W Blue LED, 4 h, rt | dr > 20:1; 25% ^e |
| 6 | [Ir(ppy) ₂ (dtbbpy)]PF ₆ (2.5 mol %), Et ₃ N (2.0 equiv) DMF, 90 W Blue LED, 4 h, rt | dr > 20:1; 35% ^e |
| 7 | [Ir(ppy) ₂ (dtbbpy)]PF ₆ (2.5 mol %), DIPEA (5 equiv), DMSO Hantzsch ester (3 equiv), 90 W Blue LED, 3 h, rt | dr > 20:1; 64% ^e |

^aReactions conducted on 1.2 equiv of 8. ^bIsolated yield after purification by silica gel chromatography. ^c28a as product. ^d28b as product. ^e28 as product.



Synthesis of compound 28



To a stirred solution of **7** (50.0 mg, 0.192 mmol) and **8** (70.1 mg, 0.231 mmol) in DMSO (2.0 mL) was added DIPEA (124.0 mg, 0.960 mmol) and Hantzsch ester (146.0 mg, 0.576 mmol) at rt under nitrogen atmosphere, followed by addition of $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (5.3 mg, 0.006 mmol), and the resultant mixture was stirred under Blue LED (90 W, kessil A360We) for 4 h. The reaction mixture was quenched with water (25 mL), and extracted with EtOAc (2 x 25 mL). The combined organic layers were washed brine (30 mL), and dried over sodium sulfate. The solvent of extract was concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (petroleum ether : EtOAc = 2:1 to 1:1) to give a yellowish oil, which was purified again by a flash chromatography on silica gel (CH_2Cl_2 : EtOAc = 20:1 to 4:1) to give **28** (54.1 mg, 64%) as yellowish oil.