DUDOGNON Yohan – 04/02/2016

Expedient Iron-Catalyzed C-H Allylation/Alkylation by Triazole Assistance with Ample Scope

G. Cera, T. Haven, L. Ackermann, *Angew. Chem. Int. Ed.*, **2016**, *55*, 1484.

DOI: 10.1002/anie.201509603

What is it about ?

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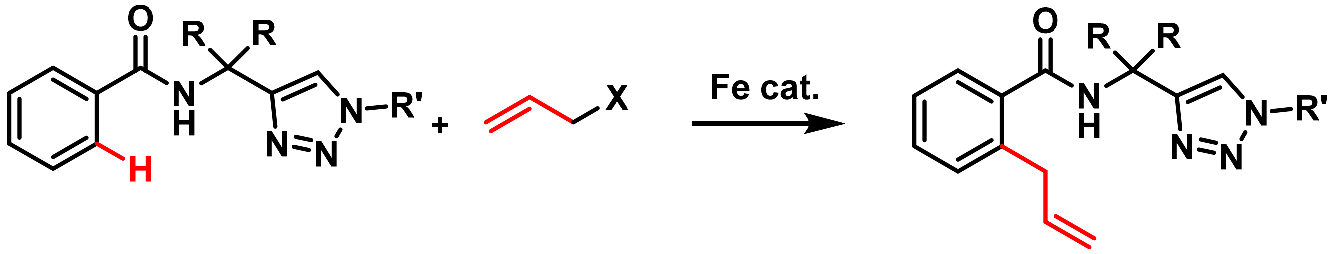
Allylation



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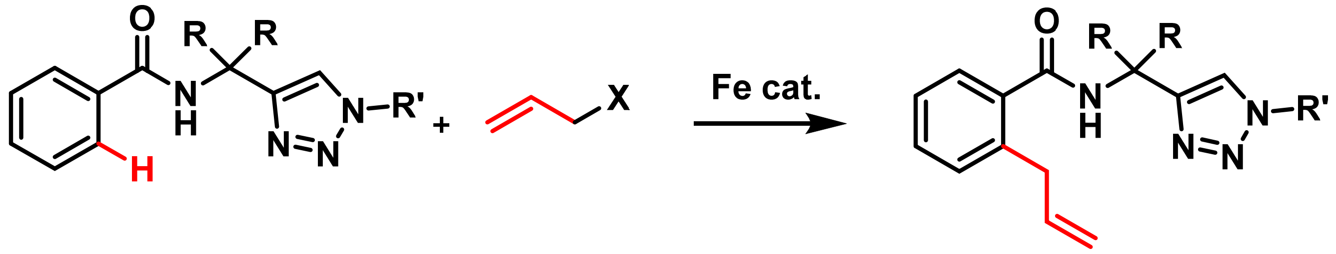
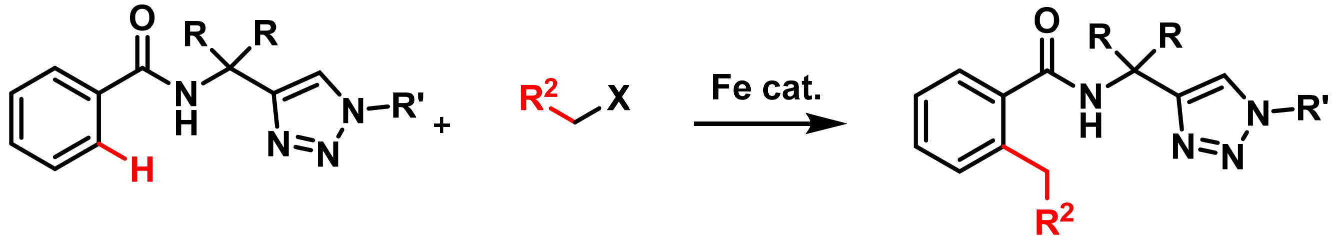


Alkylation



YD2

State of art - Functionalisation of aromatics

Friedel Crafts reactions: Discovered by Charles Friedel and James Crafts in 1877

Last review on FC alkylation: M. Rueping and al. *Beilstein J. Org. Chem.,* **2010**, *6*, 6.

Diapositive 5

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Since then: many examples of allylation/alkylation by C-H insertion with transition metals

Pd: Y. Fu and al. *J. Am. Chem. Soc.*, **2013**, *135*, 616.

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Diapositive 6

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Problems: long reaction times, high reaction temperature and/or moderate selectivites

Diapositive 7

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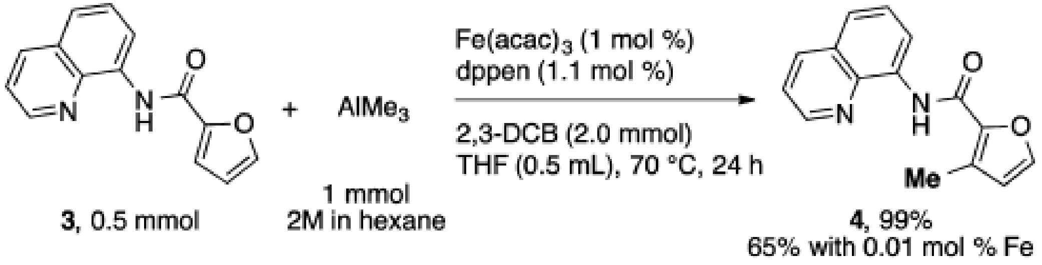
YD2

State of art - Functionalisation of aromatics

Uses of a bidentate directing group:

N. Chatani and al. *Angew. Chem. Int. Ed.*, **2013**, *52*, 11726.
E. Nakamura and al. *J. Am. Chem. Soc.*, **2015**, *137*, 7660.



Diapositive 8

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YD2

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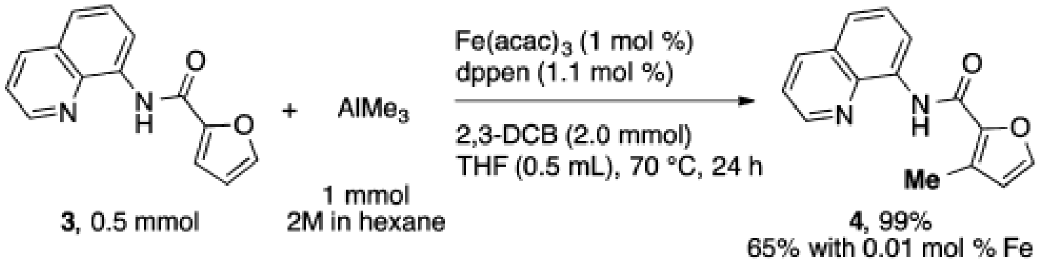

Drawbacks:

Transformations restricted to the **Amino-Quinoline** motif
Limited scope
Removal under **harsh conditions** (conc. HCl 130 °C)

Diapositive 9

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YD2

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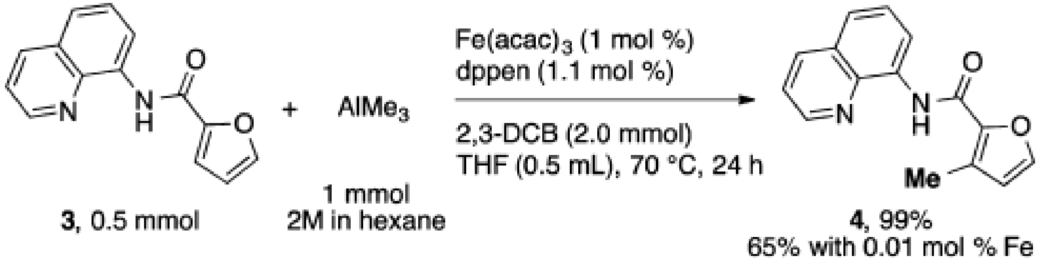

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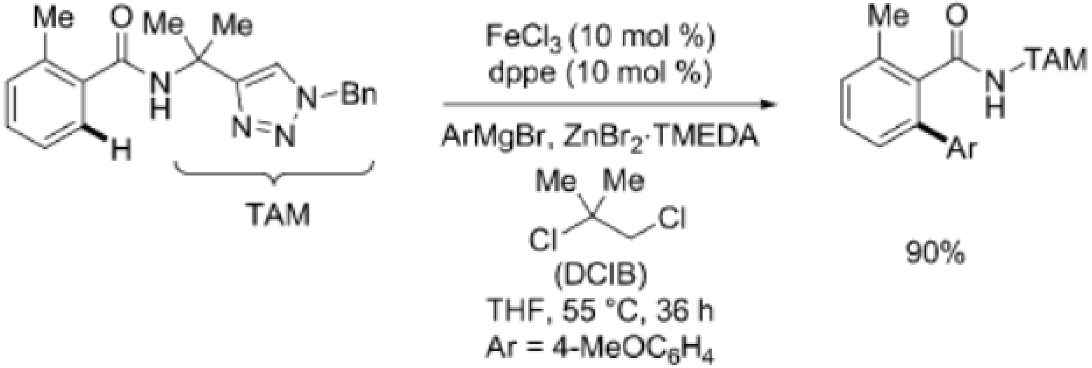
Limited scope
Removal under **harsh conditions** (conc. HCl 130 °C)

Solution: Highly modulable bidendate directing groups
Effective in promoting Fe cat. C-H transformation
Already applied for Arylation

L. Ackermann and al. *Angew. Chem. Int. Ed.*, **2014**, *53*, 3868.



Diapositive 10

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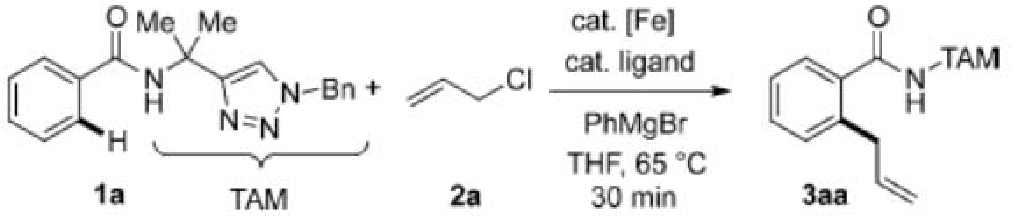
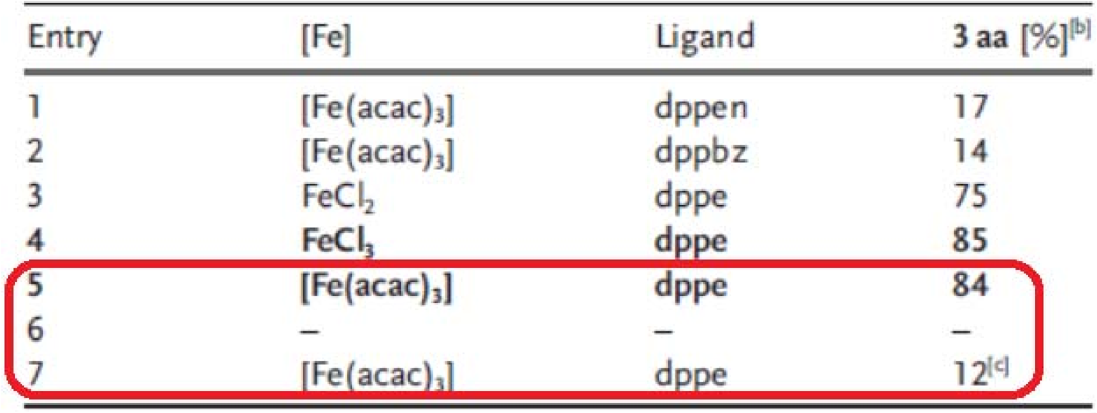
Screening of catalyst





Entry	[Fe]	Ligand	3 aa [%][b]
1	[Fe(acac)$_3$]	dppen	17
2	[Fe(acac)$_3$]	dppbz	14
3	FeCl$_2$	dppe	75
4	**FeCl$_3$**	**dppe**	**85**
5	**[Fe(acac)$_3$]**	**dppe**	**84**
6	–	–	–
7	[Fe(acac)$_3$]	dppe	12[c]

[Fe(acac)$_3$] + dppe ligand turned out to be the best catalytic system

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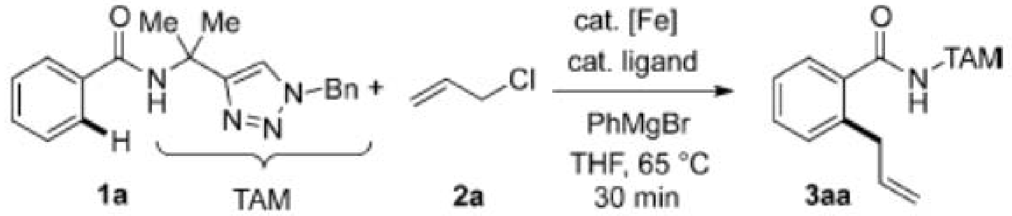
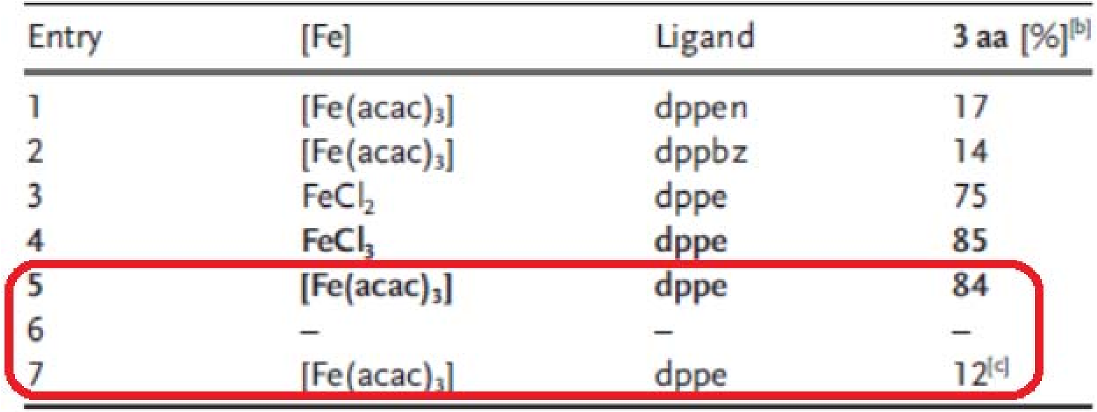


1a 2a 3aa



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No conversion without catalyst

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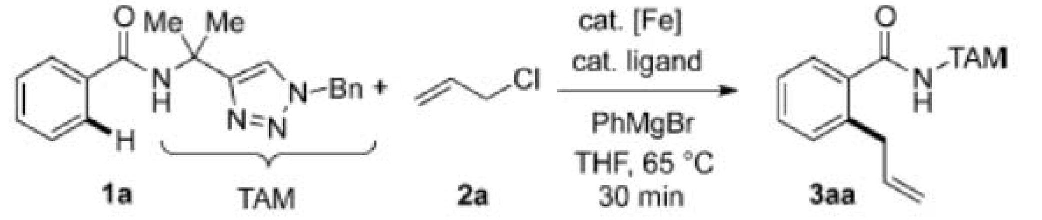

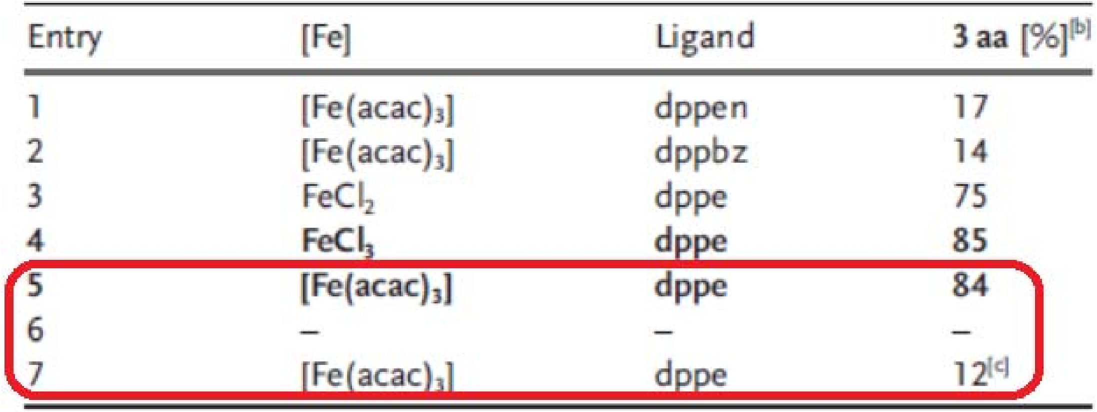

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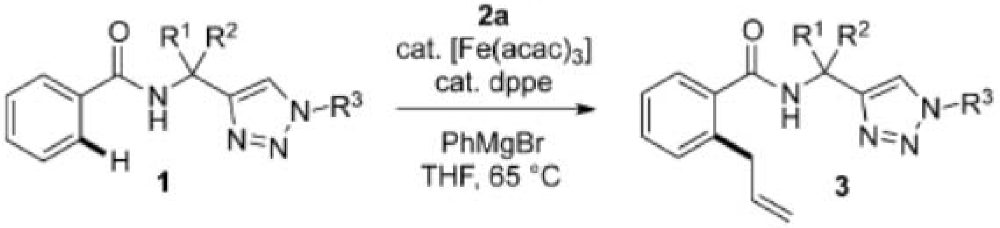
No conversion without catalyst

Amino-Quinoline as directing-group was ineffective

Substitution in the TriAzole Moiety (TAM)



Entry	R^1	R^2	R^3	**3**
1	-$(CH_2)_5$-		Bn	**3ba**: 64%
2	Me	Me	*n*Pr	**3ca**: 77%
3	Me	Me	PMP	**3da**: 78%
4	H	H	*n*Hex	**3ea**: –

Spiro substitution gives acceptable yield

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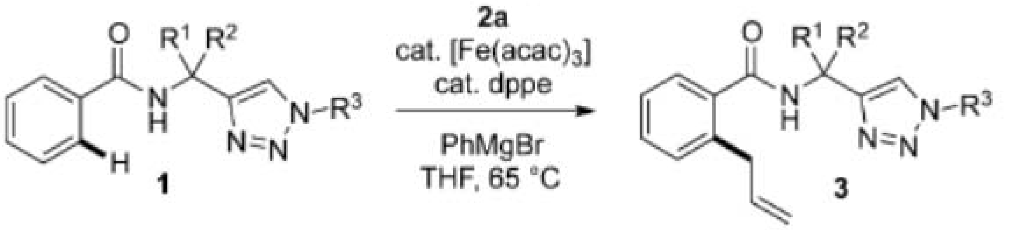

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N-alkylated or N-arylated triazoles provides good yields

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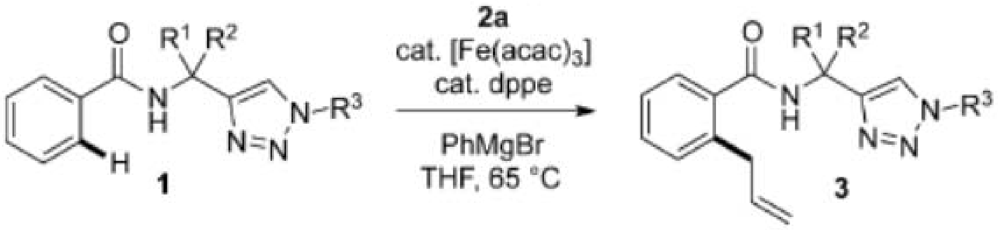

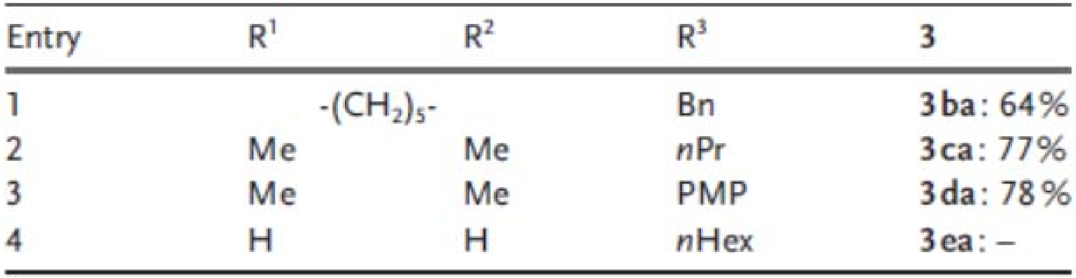

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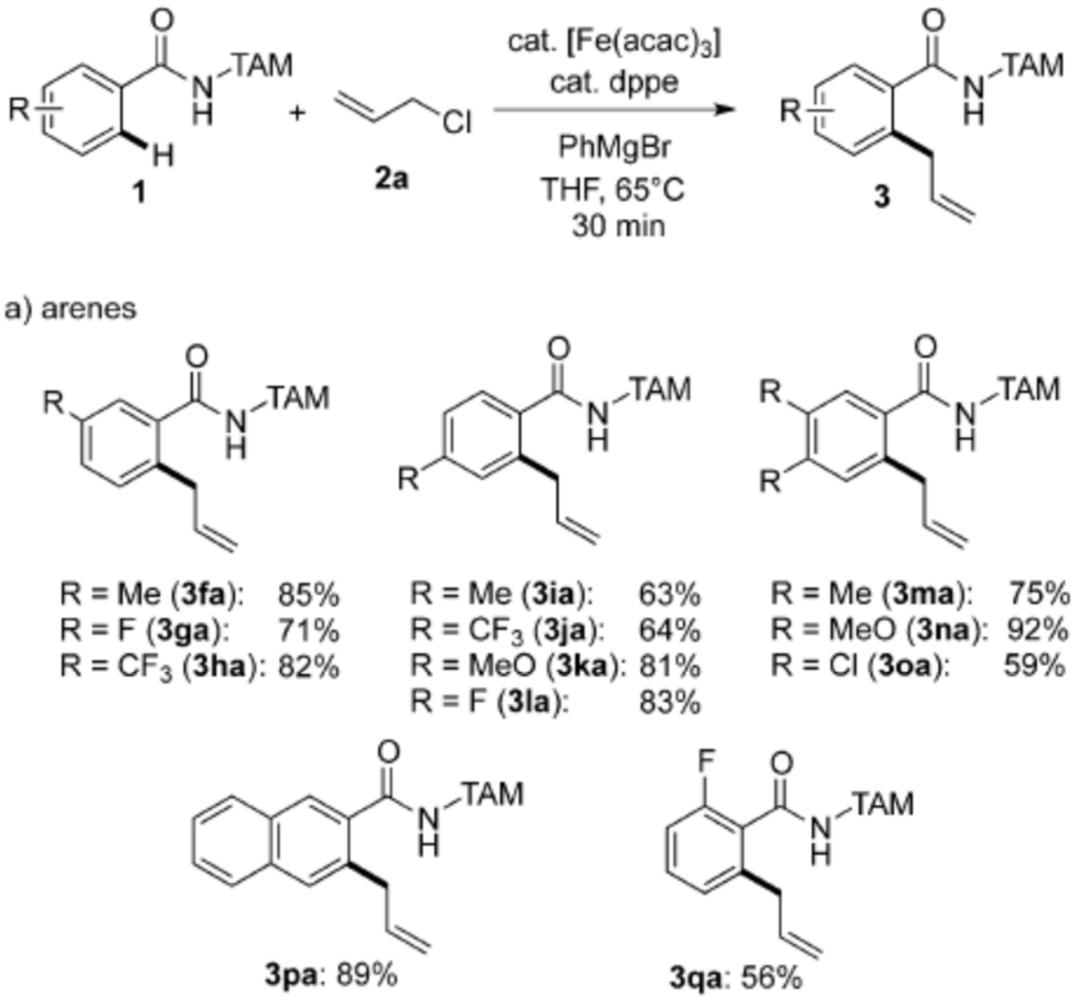
Spiro substitution gives acceptable yield

N-alkylated or N-arylated triazoles provides good yields

Substitution in benzylic position is necessary

Substrate scope



a) arenes

R = Me (**3fa**): 85%
R = F (**3ga**): 71%
R = CF_3 (**3ha**): 82%

R = Me (**3ia**): 63%
R = CF_3 (**3ja**): 64%
R = MeO (**3ka**): 81%
R = F (**3la**): 83%

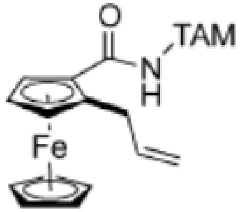
R = Me (**3ma**): 75%
R = MeO (**3na**): 92%
R = Cl (**3oa**): 59%

3pa: 89%

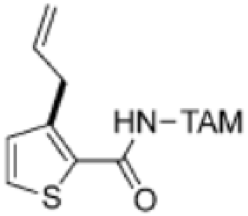
3qa: 56%

Substrate scope

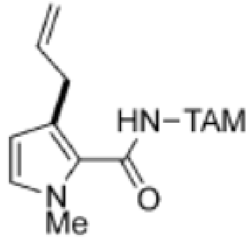
b) ferrocene and heteroarenes



3ra: 47%



3sa: 85%



3ta: 69%

Allylation of **heteroaromatics** was possible and site-selective

Diapositive 18

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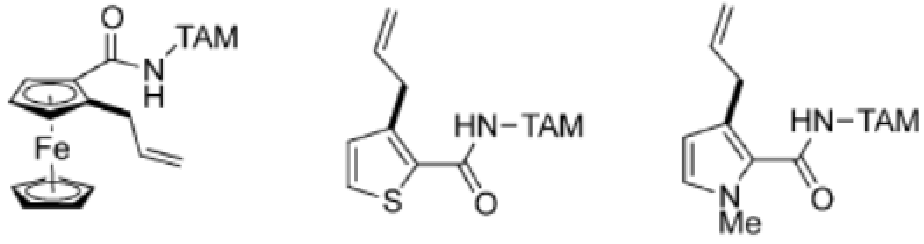
Substrate scope

b) ferrocene and heteroarenes



3ra: 47% **3sa**: 85% **3ta**: 69%

Allylation of **heteroaromatics** was possible and site-selective

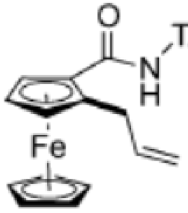
Unprecedented synthesis of **ferrocenyl derivatives**

Diapositive 19

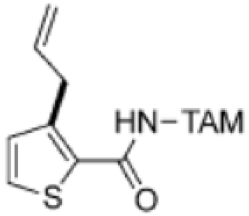
YD1 Yohan Dudognon; 31/01/2016

Substrate scope

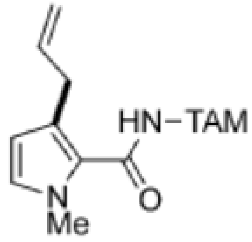
b) ferrocene and heteroarenes



3ra: 47%

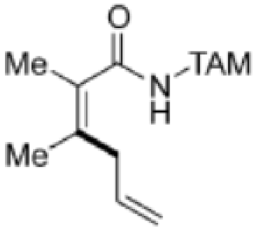


3sa: 85%

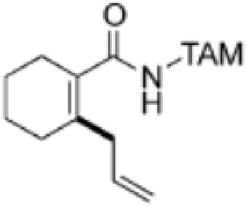


3ta: 69%

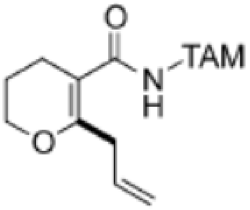
c) alkenes



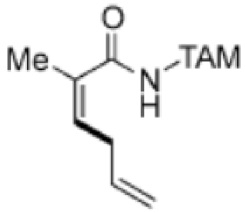
3ua: 58%



3va: 68%



3wa: 81%



3za: 62%

Allylation of **heteroaromatics** was possible and site-selective

Unprecedented synthesis of **ferrocenyl derivatives**

Applicable to **alkenes** (first example)

Diapositive 20

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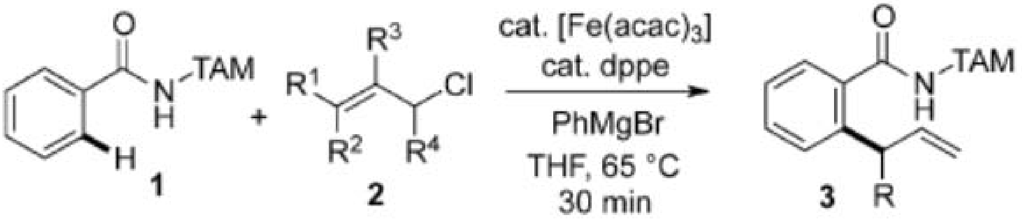
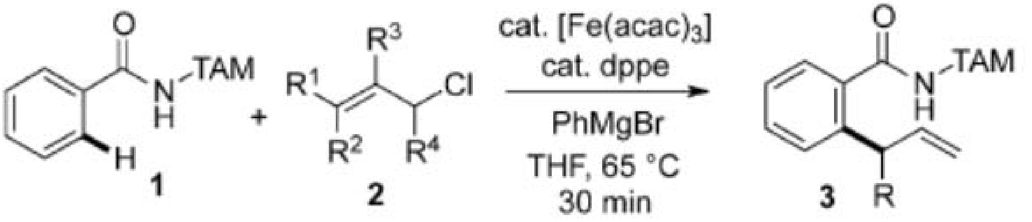
Scope - Allyl chloride



R^1 = Me, R^2, R^3, R^4 = H (**2b**) **3ab**: R = Me, 80% (b/l 4.2:1)
R^1, R^2, R^3 = H, R^4 = Me (**2c**) **3ac**: R = Me, 75% (b/l 2.5:1)
R^1 = *n*Pr, R^2, R^3, R^4 = H (**2d**) **3ad**: R = *n*Pr, 71% (b/l 3.1:1)
R^1 = *n*Bu, R^2, R^3, R^4 = H (**2e**) **3ae**: R = *n*Bu, 65% (b/l 3.2:1)
R^1 = *i*Pr, R^2, R^3, R^4 = H (**2f**) **3af**: R = *i*Pr, 62% (b/l 2.0:1)
R^1, R^3, R^4 = H, R^2 = Et (**2g**) **3ag**: R = Et, 58% (b/l 5.5:1)

Comparaison of **branched vs linear product**

Scope - Allyl chloride



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Similar results if the **Me** is on **R_1** or **R_4 position**

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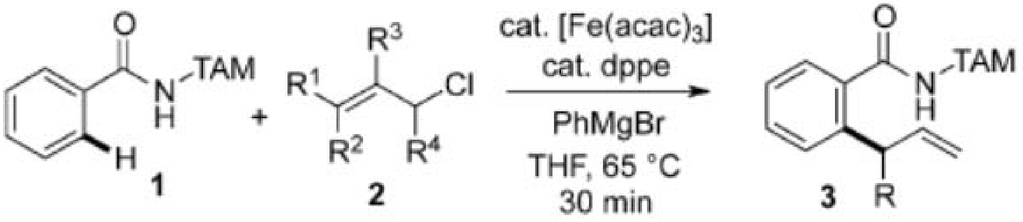

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Comparaison of **branched vs linear product**

Similar results if the **Me** is on **R_1** or **R_4 position**

Strong support for the formation of a **η^3-allyl intermediate**

Mechanistic Study

- Strong support for the formation of a **η^3-allyl intermediate**

- **Competition experiments with isotopically labeled substrates:**

Kinetic isotopic effects of $k_H/k_D = 2$

Conclusion: C-H cleavage occurs as or prior the turnover-limiting step

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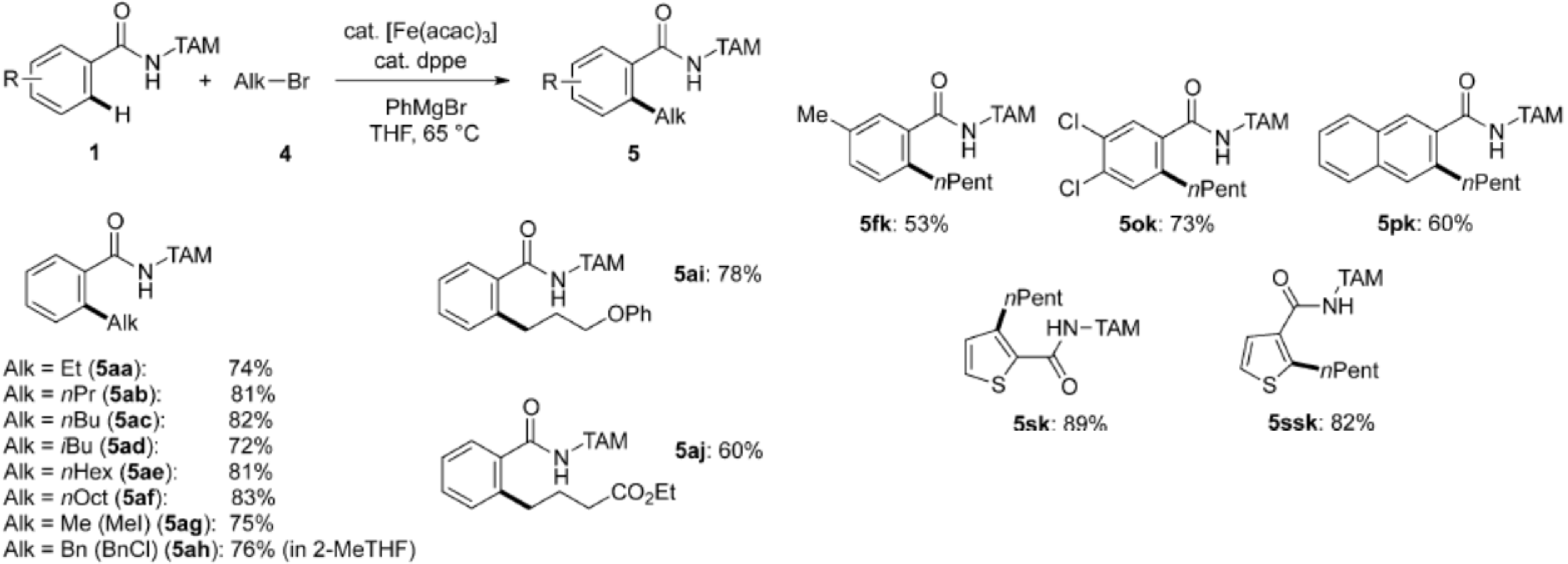
Final conclusion: **Mechanism is not likely a Radical-based reaction**

C-H Alkylation



Alk = Et (**5aa**): 74%
Alk = *n*Pr (**5ab**): 81%
Alk = *n*Bu (**5ac**): 82%
Alk = *i*Bu (**5ad**): 72%
Alk = *n*Hex (**5ae**): 81%
Alk = *n*Oct (**5af**): 83%
Alk = Me (MeI) (**5ag**): 75%
Alk = Bn (BnCl) (**5ah**): 76% (in 2-MeTHF)

5ai: 78%

5aj: 60%

5fk: 53%

5ok: 73%

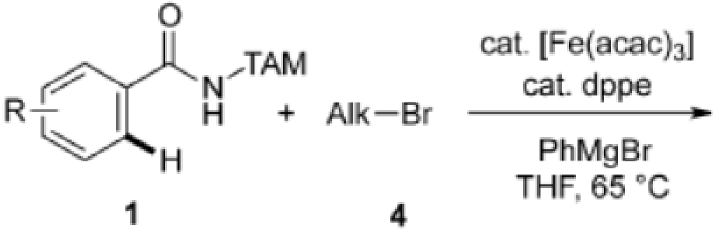
5pk: 60%

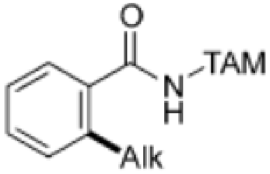
5sk: 89%

5ssk: 82%

C-H alkylation was also possible different alkyl halides

C-H Alkylation





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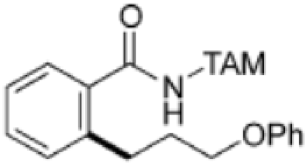
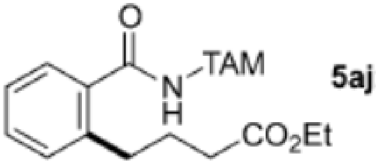
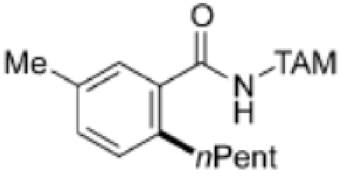


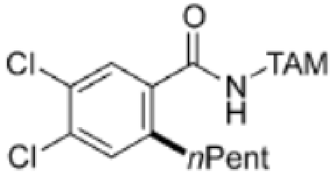
5ai: 78%



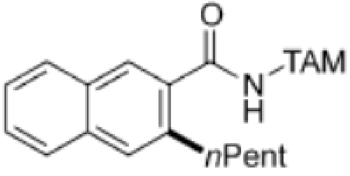
5aj: 60%



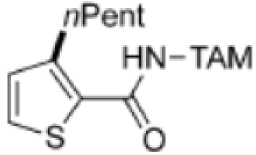
5fk: 53%



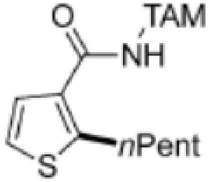
5ok: 73%



5pk: 60%



5sk: 89%

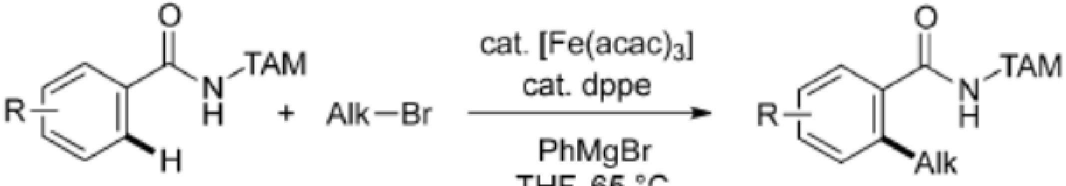


5ssk: 82%

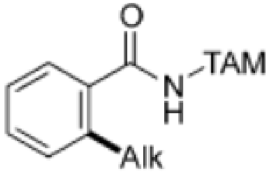
C-H alkylation was also possible different alkyl halides

Good yield and excellent monoalkylation selectivities

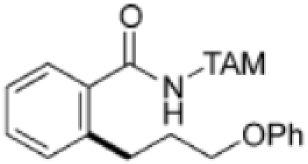
C-H Alkylation



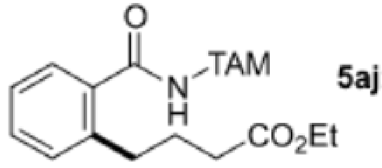
1 **4** **5**



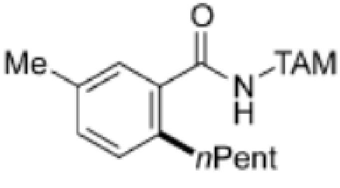
Alk = Et (**5aa**): 74%
Alk = *n*Pr (**5ab**): 81%
Alk = *n*Bu (**5ac**): 82%
Alk = *i*Bu (**5ad**): 72%
Alk = *n*Hex (**5ae**): 81%
Alk = *n*Oct (**5af**): 83%
Alk = Me (MeI) (**5ag**): 75%
Alk = Bn (BnCl) (**5ah**): 76% (in 2-MeTHF)



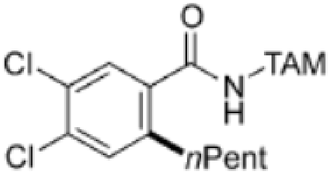
5ai: 78%



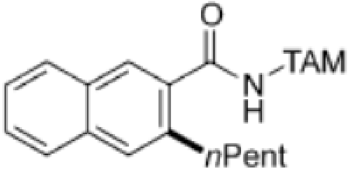
5aj: 60%



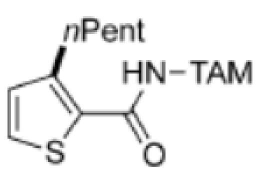
5fk: 53%



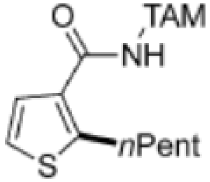
5ok: 73%



5pk: 60%



5sk: 89%



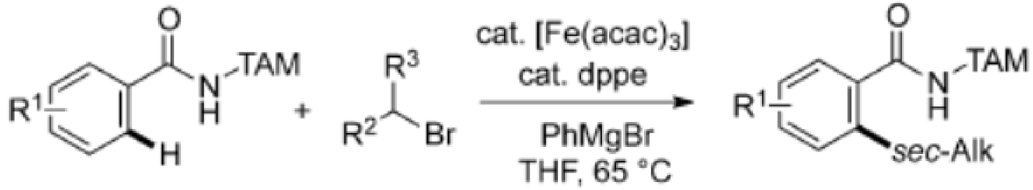
5ssk: 82%

C-H alkylation was also possible different alkyl halides

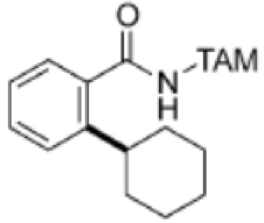
Good yield and excellent monoalkylation selectivities

Robustness of the catalyst: tolerance of ether, esters, substituted arenes and hetereoarenes

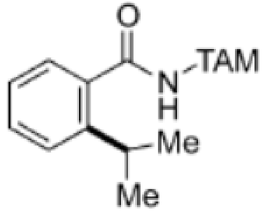
C-H alkylation with secondary alkyl halides



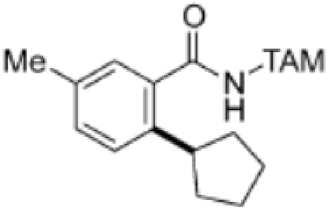
1 **6** **7**



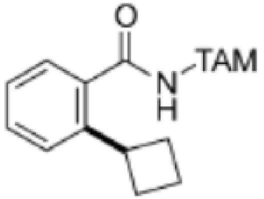
7ad: 51%



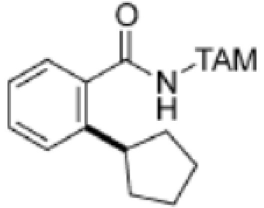
7ae: 50%
(in 2-MeTHF)



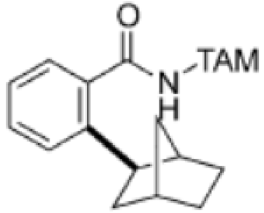
7fb: 54%



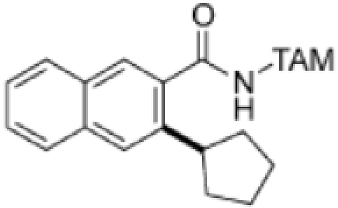
7aa: 54%



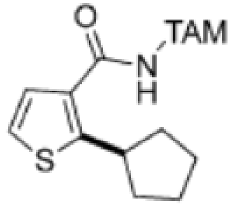
7ab: 52%



7ac: 59%



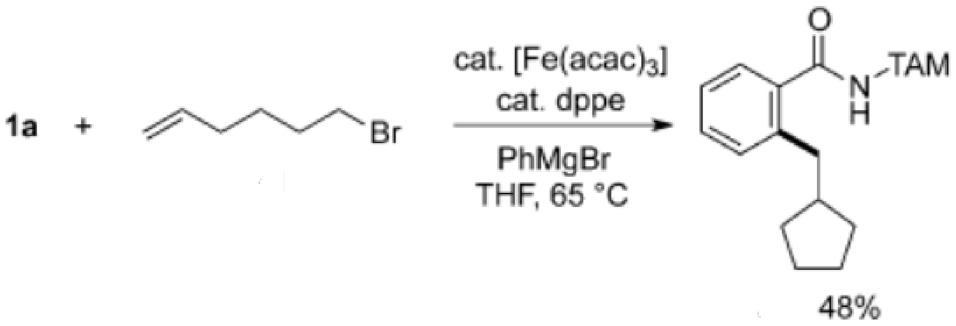
7pb: 57%



7ssb: 53%

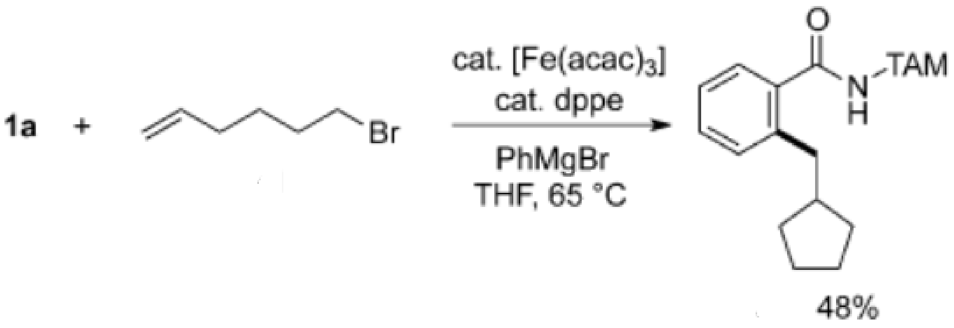
More challenging **secondary alkyl halides** were also appropriate substrates

Mechanistic Study

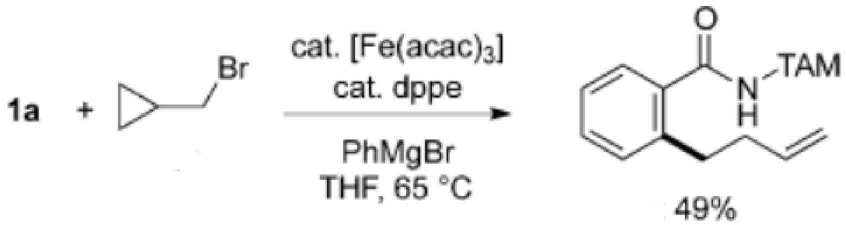


Formation of the cyclized product

Mechanistic Study

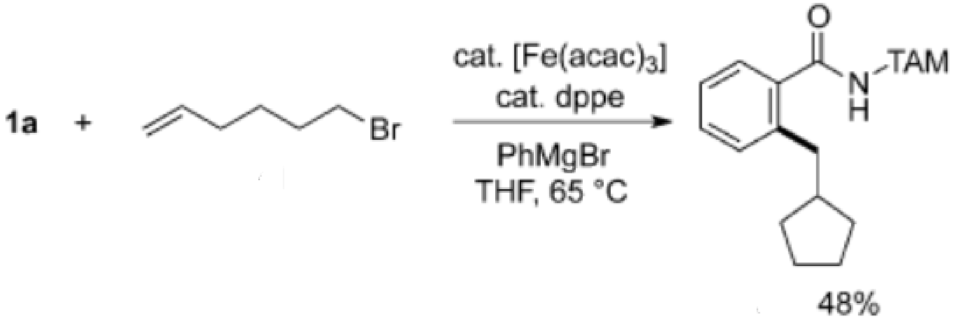


Formation of the cyclized product

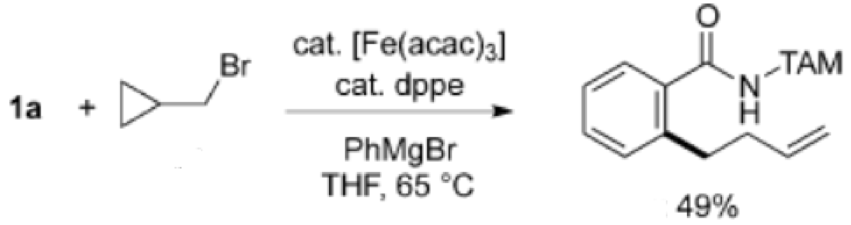


Formation of the homoallylated product

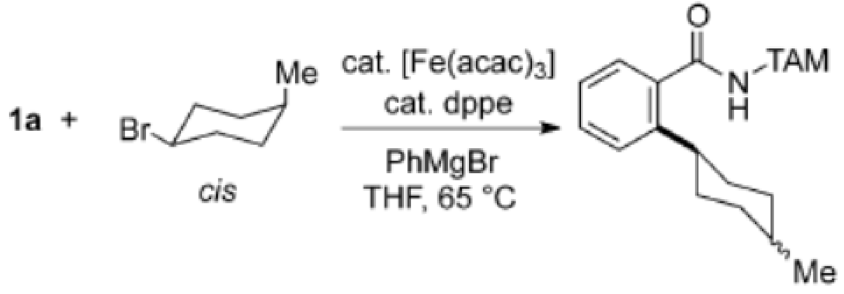
Mechanistic Study



Formation of the cyclized product



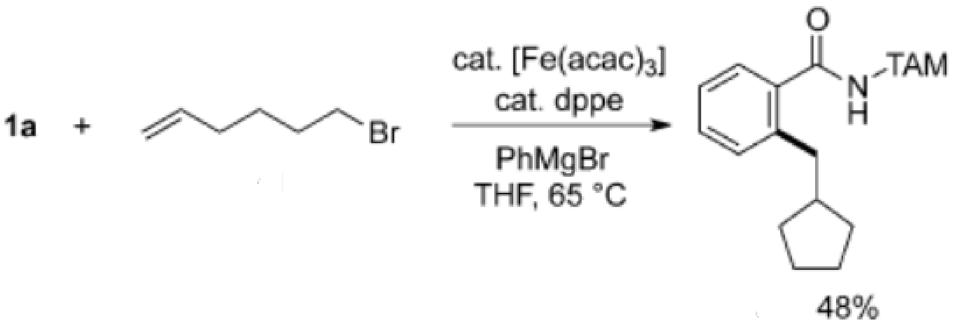
Formation of the homoallylated product



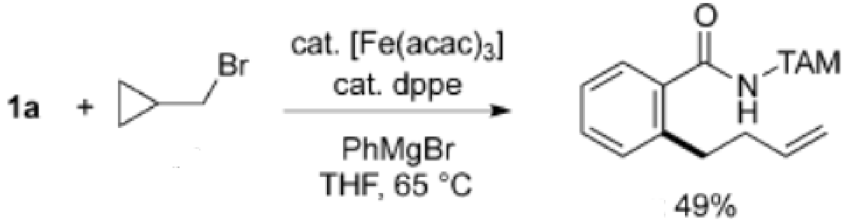
Erosion of the stereochemical information

TEMPO decreases the conversion

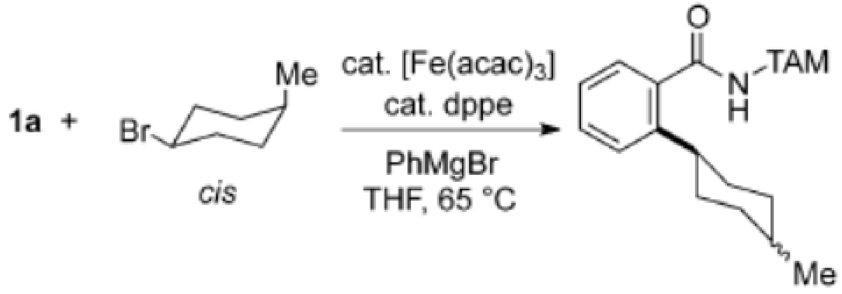
Mechanistic Study



Formation of the cyclized product



Formation of the homoallylated product

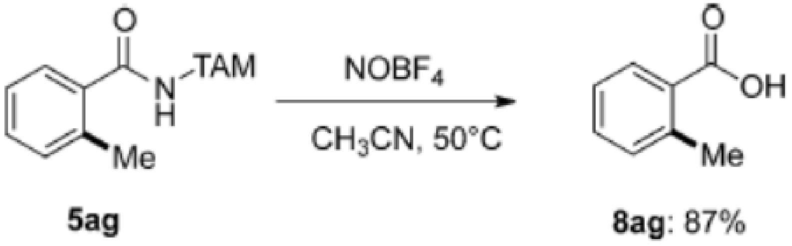


Erosion of the stereochemical information

TEMPO decreases the conversion

Rationalisation: Single-electron-transfert-type reaction mechanism

Removal of the TAM directing group



Novel protocol to remove the directing group

Very mild condition compared to other method to remove directing group

Furnish the desired carboxylic acid in high yields

Conclusion

First unified strategy for **iron**-catalysed **C-H allylation** and **alkylation**

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Triazole assistance enables site-selective C-H functionalization of arenes, heteroarenes and alkenes

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Triazole assistance enables site-selective C-H functionalization of arenes, heteroarenes and alkenes

Easily removable directing group under mild conditions

Conclusion

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Triazole assistance enables site-selective C-H functionalization of arenes, heteroarenes and alkenes

Easily removable directing group under mild conditions

Mechanistic studies: Likely **not a radical mechanism** for **allylation**
SET mechanism for **alkylation**

Thank you for your attention !