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Enantioselective Synthesis of Janus Kinase Inhibitor INCB018424 via an Organocatalytic Aza-Michael Reaction

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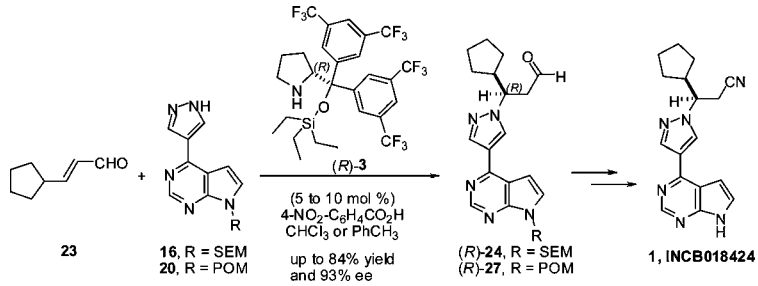
ABSTRACT



An enantioselective synthesis of INCB018424 via organocatalytic asymmetric aza-Michael addition of pyrazoles (16 or 20) to (*E*)-3-cyclopentylacrylaldehyde (23) using diarylprolinol silyl ether as the catalyst was developed. Michael adducts (*R*)-24 and (*R*)-27 were isolated in good yield and high ee and were readily converted to INCB018424.

Janus kinases (JAKs) are crucial signal transducers for a variety of cytokines, growth factors, and interferons.[1−3] Inhibition of JAKs has advanced the basic and clinical studies of tyrosine kinase inhibitors as anticancer, anti-inflammation, and antiallograft rejection agents. It has been suggested that inhibition of JAKs can be beneficial for patients with myeloproliferative disorders[4] and inflammatory conditions such as rheumatoid arthritis.[5] INCB018424 was discovered as an inhibitor of JAKs and is currently under clinical development.[6]

In view of its structural features, we envisioned that INCB018424 could be prepared from suitable chiral β-amino carbonyl compounds. The catalytic asymmetric aza-Michael reaction is a powerful method for the synthesis of these compounds.[7] Although the use of transition metal complexes with chiral ligands is well-documented,[8] the use of organocatalysts in asymmetric aza-Michael reactions offers a unique advantage by not requiring metal removal from drug substance in large scale production.

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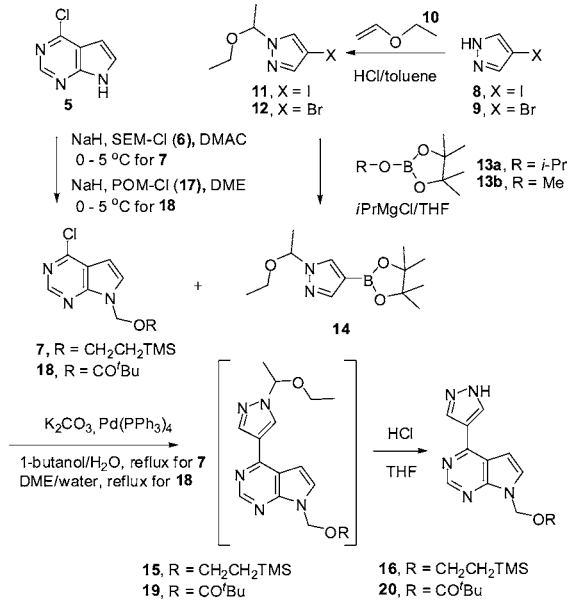
In organocatalytic aza-Michael reactions, the acceptors are activated either by hydrogen bonding of the organocatalysts to the carbonyl group of the acceptors[9] or by imminium formation between α,β-unsaturated aldehydes and the organocatalysts.[10] Jørgensen reported the successful use of proline-derived organocatalysts in the addition of nitrogen-containing heterocycles such as triazoles and tetrazoles to α,β-unsaturated aldehydes.[11] We envisioned that the extension of Jørgensen's chemistry[11] to the aza-Michael addition of substituted pyrazoles **16** or **20** to aldehyde (**23**) using suitable organocatalysts would provide an efficient asymmetric synthetic route to INCB018424 (**1**) (Scheme 2).

The synthesis of Michael donor **16** via a Suzuki coupling of protected pyrazole pinacol borate (**14**) and the protected chlorodeazapurine (**7**) is depicted in Scheme 1. 4-Iodo-1*H*-pyrazole (**8**) or 4-bromo-1*H*-pyrazole (**9**) was treated with ethyl vinyl ether (**10**) to give the protected pyrazoles **11** and **12** respectively. Halogen-magnesium exchange of **11** or **12** followed by addition of borate **13a** or **13b** afforded the pyrazole pinacol borate **14** in good yield. Treatment of compound **5** with NaH and 2-(trimethylsilyl)ethoxyethyl chloride (SEM-Cl, **6**) afforded the SEM-protected **7** in 89% yield. Suzuki coupling of **7** with pyrazole pinacol borate **14** furnished intermediate **15** which was hydrolyzed in situ to give the key Michael donor **16** in 82% yield for two steps. The POM-protected Michael donor **20** was similarly prepared. Treatment of the sodium anion of compound **5** with pivaloyloxymethyl chloride (POM-Cl, **17**) afforded intermediate **18** in 91% yield. Suzuki coupling of **18** and **14** afforded **20** in 91% yield via **19**.

Scheme 1. Synthesis of Michael Donors **16** and **20**



On the basis of the mechanism proposed by Jørgenson,[11] it was conceivable that the enantioselectivity could be improved by the modulation of steric hindrance of the organocatalyst. Catalyst (*R*)-**2** was purchased from a commercial source and catalysts (*R*)-**3** and (*R*)-4 were synthesized according to literature procedures (see experimental details in the Supporting Information).[12]

Wittig olefination of cyclopentanecarbaldehyde (**21**) provided **23** as shown in Scheme 2.[13] The olefin **23** was shown by ^{1}H NMR to be exclusively in the (*E*) configuration. However, it was contaminated with about 14% of the dienal **23a**. The impurity **23a** could be removed by preparative HPLC but not by silica gel flash chromatography. As a control experiment, pure dienal **23a** was reacted with **16**. Very low conversion to the corresponding Michael adduct was observed (less than 10% over 24 h under the same conditions as described in entry 12, Table 2). This suggested the dienal impurity **23a** would not have a significant influence on the asymmetric aza-Michael addition. Since an excess amount of the Michael acceptor **23** was used in the reactions, for practical considerations, **23** was used without further purification in this study. With Michael donors (**16** and **20**), Michael acceptor **23**, and organocatalysts (*R*)-**2**, (*R*)-**3**, and (*R*)-**4**, in hand, the stage was set for the asymmetric aza-Michael reaction.

The effects of solvent, acid additive, temperature, and loading of catalyst (*R*)-**2** on the enantioselectivity and yield of the aza-Michael addition of **16** to the acceptor **23** are shown in Table 1. The reactions proceeded faster and gave adduct (*R*)-**24** in higher yields and ee in toluene and benzene (entries 2 and 3) than those in polar solvents, such as THF and 1,4-dioxane (entries 7 and 8). Acid additives, such as benzoic acid and 4-nitrobenzoic acid, accelerated the reaction (entries 2 and 12 vs 9). Lower reaction temperature gave (*R*)-**24** in slightly higher enantioselectivity (entry 1 vs 2). Higher loading of (*R*)-**2** at 20 mol% did not improve the yield or enantioselectivity (entry 1 vs 13; 11 vs 14). An excess of acceptor **23** to donor **16** gave higher yield of (*R*)-**24** (entry 11 vs 15).

The Michael addition of **16** and **23** was slower (ca. 50% conversion over 16 h) with sterically hindered catalysts (*R*)-**3** or (*R*)-**4** at 0 °C as compared to that with (*R*)-**2**. Therefore, reactions of **16** and **23** using (*R*)-**3** or (*R*)-**4** were carried out at room temperature (Table 2). The use of larger excess of **23** (5 equiv) resulted in higher yield (entries 1 and 7 vs 11). Using 5 equiv of the **23**, we compared the reaction of pure

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Table 1. Reactions of **16** using (*R*)-**2**[a]

entry	solvent	additive	*t* (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	PhMe	PhCOOH	0	18	57	88
2	PhMe	PhCOOH	rt	20	63	85
3	PhH	PhCOOH	rt	18	60	88
4	$PhCF_3$	PhCOOH	0	20	50	88
5	PhCl	PhCOOH	rt	26	47	85
6	cyclohex	PhCOOH	rt	120	35	86
7	THF	PhCOOH	rt	54	49	80
8	dioxane	PhCOOH	rt	53	58	82
9	PhMe	no addditive	rt	62	73	83
10	PhH	no addditive	40	21	72	81
11	PhMe	4-NO_2-C_6H_4COOH	0	20	61	87
12	PhH	4-NO_2-C_6H_4COOH	rt	47	65	82
13[d]	PhMe	PhCOOH	0	20	54	90
14[d]	PhMe	4-NO_2-C_6H_4COOH	0	18	61	88
15[e]	PhMe	4-NO_2-C_6H_4COOH	0	26	39	89

[a] Reaction condition: unless specified, all reactions were carried out on 0.5 mmol scale with 1 equiv of **16** and 1.5 equiv of aldehyde **23** in the presence of 10 mol % of organocatalyst (*R*)-**2** and 10 mol % of acid additive in 2.5 mL of solvent. [b] Isolated yields. [c] Determined by chiral HPLC analysis of the corresponding nitrile (*R*)-**25**, conditions: Chiralcel OD-H (4.6 × 250 mm, 5 μm particle size); 1 mL/min; rt; 220 nm; mobile phase, 10% (v/v) ethanol and 90% (v/v) hexanes. [d] Organocatalyst (20 mol %) (*R*)-**2** was used. [e] **16** (1.5 equiv) and 1 equiv of aldehyde **23** used.

Table 2. Reactions of **16** using (*R*)-**3** or (*R*)-**4**[a]

entry	**23** (equiv)	cat.	concn (M)	additive	time (h)	yield (%)[b]	ee (%)[c]
1	1.5	(*R*)-**3**	0.2	4-NO_2-PhCOOH	24	65	90
2	1.5	(*R*)-**3**	0.2	PhCOOH	45	63	91
3	1.5	(*R*)-**3**	0.25	2-F-C_6H_4COOH	30	63	87
4	1.5	(*R*)-**3**	0.25	4-F-C_6H_4COOH	30	60	91
5	1.5	(*R*)-**3**	0.25	3,5-$(NO_2)_2$-C_6H_3COOH	23	61	84
6	1.5	(*R*)-**3**	0.25	2,4-$(NO_2)_2$-C_6H_3COOH	23	52	70
7	2	(*R*)-**3**	0.25	4-NO_2-C_6H_4COOH	24	68	89
8	3	(*R*)-**3**	0.25	4-NO_2-C_6H_4COOH	21	78	89
9	4	(*R*)-**3**	0.2	4-NO_2-C_6H_4COOH	24	80	88
10	5	(*R*)-**3**	0.25	4-NO_2-C_6H_4COOH	21	80	88
11	5	(*R*)-**3**	0.2	4-NO_2-C_6H_4COOH	23	83	88
12	5	(*R*)-**3**	0.1	4-NO_2-C_6H_4COOH	24	84	89
13[d]	5	(*R*)-**3**	0.1	4-NO_2-C_6H_4COOH	21	74	89
14	5	(*R*)-**3**	0.5	4-NO_2-C_6H_4COOH	22	74	87
15	5	(*R*)-**3**	0.25	4-F-C_6H_4COOH	27	78	89
16	5	(*R*)-**2**	0.2	4-NO_2-C_6H_4COOH	22	79	83
17	5	(*R*)-**4**	0.2	4-NO_2-C_6H_4COOH	22	75	90

[a] Reaction condition: all reactions were carried out on 0.5 mmol scale with 1 equiv of **16** in the presence of 10 mol % of organocatalyst and 10 mol % of acid additive in toluene at rt. [b] Isolated yields. [c] Determined by chiral HPLC analysis of corresponding nitrile (*R*)-**25**, same conditions as described in Table 1. [d] Pure aldehyde **23** (contained no **23a**) was used.

23 (obtained by preparative HPLC) with that of unpurified **23** (contained 14% of **23a**) (entry 12 vs 13). The ee of the adducts were identical and yields were similar, confirming the low reactivity of the impurity **23a**.

Under identical reaction conditions (entries 11, 16, 17), sterically hindered catalysts (*R*)-**3** and (*R*)-**4** gave higher enantioselectivity (88% ee and 90% ee respectively) than (*R*)-**2** (83% ee). The use of stronger acid additives gave faster reactions as illustrated by benzoic acids substituted with electron withdrawing fluoro-(entries 3, 4) or nitro-groups (entries 1, 5, 6) compared to benzoic acid (entry 2). Interestingly, further increase in acidity from 4-nitrobenzoic acid (entry 1) to dinitrobenzoic acids (entry 5, 6) resulted in lower enantioselectivities.

Applying the optimized conditions (entry 12, Table 2), adduct (*R*)-**24** was obtained in 84% yield at 89% ee. (*R*)-**24** was treated with aqueous ammonia to give the corresponding imine which was subsequently oxidized by iodine to provide the nitrile (*R*)-**25** in 82% yield.[14] The SEM protection group in (*R*)-**25** was removed using $LiBF_4$ and aqueous ammonia to give INCB018424 (**1**) in 84% yield.[15] The enantiomeric purity was maintained during this reaction.

Using the optimized conditions for the reaction between **16** and **23**, we conducted the aza-Michael addition of the POM-protected **20** to aldehyde **23** (Scheme 2 and Table 3).

Scheme 2. Aza-Michael Reactions of **16** or **20** with **23**

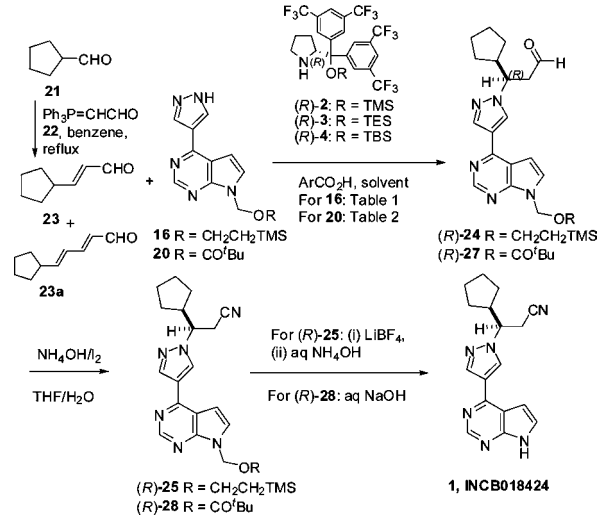


Table 3. Reactions of **20** using (*R*)-**2**, (*R*)-**3** or (*R*)-**4**[a]

entry	cat. (equiv)	solvent	concn (M)	*t* (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	(*R*)-**3** (0.1)	PhMe	0.2	rt	46	75	89
2	(*R*)-**4** (0.1)	PhMe	0.25	rt	46	65	90
3	(*R*)-**4** (0.1)	$CHCl_3$	0.25	0	24	69	93
4	(*R*)-**3** (0.1)	$CHCl_3$	0.25	0	46	75	92
5	(*R*)-**2** (0.1)	$CHCl_3$	0.25	0	22	81	87
6	(*R*)-**3** (0.1)	$CHCl_3$	0.25	rt	24	72	90
7	(*R*)-**3** (0.05)	$CHCl_3$	0.25	rt	23	80	90
8[d]	(*R*)-**3** (0.05)	$CHCl_3$	0.25	rt	21	78	89

[a] Reaction condition: all reactions were carried out on 0.5 mmol scale with 1 equiv of **20** and 5 equiv of aldehyde **23** in the presence of 5−10 mol % of organocatalyst and 5−10 mol % of 4-nitrobenzoic acid. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel OD-H) of corresponding nitrile (*R*)-**28**, same conditions as described in Table 1. [d] Pure aldehyde **23** (contained no **23a**) was used.

Due to the low solubility of **20** in toluene, lower yield and slower reactions (entries 1, 2) were observed as compared

to the reaction between **16** and **23**. Changing the solvent to chloroform gave faster reactions which could be run at 0 °C (entry 3). The yield could be improved without sacrificing the ee by lowering catalyst loading to 5 mol% (entry 6 vs 7). The trend of higher enantioselectivity with increased steric hindrance of the organocatalyst was again observed in the reactions between **20** and **23** (entries 3, 4, 5). The purity of **23** has no impact on the ee or yield of (*R*)-**27** (entry 7 vs 8).

The adduct (*R*)-**27** was obtained in 80% yield and 90% ee under the optimized conditions (entry 7, Table 3). The aldehyde group in (*R*)-**27** was readily converted to the corresponding nitrile (*R*)-**28** in 87% yield. The POM group was removed by NaOH in methanol to furnish INCB018424 quantitatively (Scheme 2). The enantiomeric purity was also maintained during the conversion of (*R*)-**28** to INCB018424.

An alternative approach for the synthesis of INCB018424 utilized the aza-Michael reaction of 4-bromopyrazole (**9**) with **23** which gave adduct (*R*)-**29** in 85% yield and 84% ee. (entry 4, Table 4). (*R*)-**29** was readily converted to the nitrile (*R*)-**30** in 79% yield. (*R*)-**30** was subsequently converted to INCB018424 by a Suzuki coupling of the in situ generated pinacol borate (*R*)-**32** with **5** in 64% yield for two steps (Scheme 3).

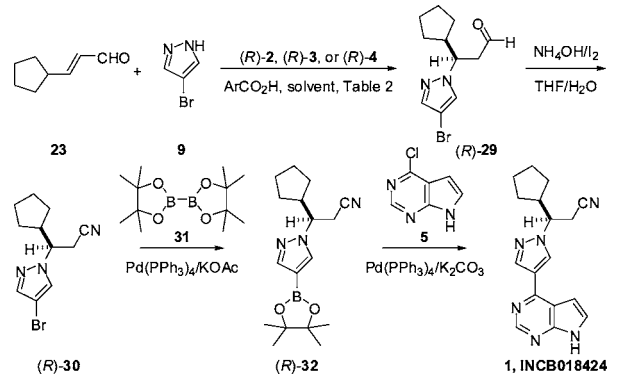
Table 4. Reactions of **9** using (*R*)-**2**, (*R*)-**3** or (*R*)-**4**[a]

entry	**23** (equiv)	cat.	concn (M)	additive	time (h)	yield (%)[b]	ee (%)[c]
1	5	(*R*)-**2**	0.25	PhCOOH	21	79	69
2	5	(*R*)-**3**	0.25	PhCOOH	24	74	82
3	5	(*R*)-**4**	0.25	PhCOOH	23	74	85
4	5	(*R*)-**4**	0.25	4-NO_2-C_6H_4COOH	22	85	84
5	1.5	(*R*)-**3**	0.25	4-NO_2-C_6H_4COOH	45	74	79

[a] Reaction condition: all reactions were carried out on 1 mmol scale with 1 equiv of **9** in the presence of 10 mol % of organocatalyst and 10 mol % of acid additive in toluene at 0 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis of corresponding nitrile (*R*)-**30**, conditions: Chiralpak AD-H (4.6 × 250 mm, 5 μm particle size); 1 mL/min; rt; 220 nm; mobile phase, 15% (v/v) ethanol and 85% (v/v) hexanes.

Consistent with earlier observations, the use of bulkier catalysts (*R*)-**3** and (*R*)-**4** gave adduct (*R*)-**29** in higher ee than using (*R*)-**2** (entries 2 and 3 vs 1, Table 4). The enantiomeric purity of adduct (*R*)-**29** was determined by chiral HPLC of its corresponding nitrile (*R*)-**30**. To confirm no erosion of enantiomeric purity had occurred during the conversion of (*R*)-**29** to (*R*)-**30**, a sample of (*R*)-**29** (entry 5, Table 4) was reduced with $NaBH_4$ to its alcohol followed by treatment with *p*-chlorobenzoyl chloride. The ee of this ester was shown to be 78% by chiral HPLC, almost identical to that of (*R*)-**30** at 79%.

Scheme 3. Aza-Michael Reactions of **9** with **23**



In conclusion, we have developed an asymmetric organocatalytic aza-Michael addition of the substituted pyrazoles (**9**, **16**, or **20**) to the α,β-unsaturated aldehyde **23** using catalysts (*R*)-**2**, (*R*)-**3**, or (*R*)-**4**. Michael adducts were obtained in good yields with high ee and were readily converted to INCB018424. The use of benzoic acid or 4-nitrobenzoic acid as additive was shown to increase reaction rate. Stronger acids (e.g., dinitrobenzoic acids) were found to diminish enantioselectivity. Higher enantioselectivities were observed in reactions using the more sterically hindered organocatalysts.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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